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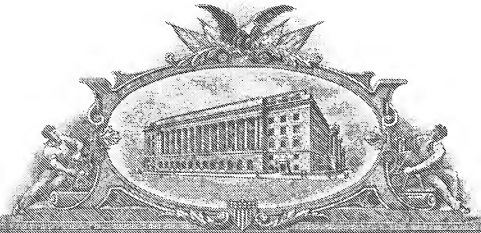

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)

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☐ Additional inventors are being named on the ____ separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

HIV Integrase Inhibitors

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OR

☐ Firm or Individual Name

Address

Address

City | State | ZIP

Country | Telephone | Fax

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification Number of Pages 138 ☐ CD(s), Number

☐ Drawing(s) Number of Sheets ☐ Other (specify)

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

☒ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number 07-1392

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted, Karen L. Prus

SIGNATURE

Date 2/11/04

TYPED or PRINTED NAME Karen L. Prus

REGISTRATION NO. (if appropriate) 39,337

Docket Number: PR60567P

TELEPHONE 919-483-2192

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): **Johns, et al.**			Docket No. **PR60567P**
Serial No. **To Be Assigned**	Filing Date **Concurrently Herewith**	Examiner	Group Art Unit

Invention: **HIV Integrase Inhibitors**

I hereby certify that this **Provisional Application**
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is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: Director of the United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 on **February 11, 2004**
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HIV INTEGRASE INHIBITORS

BACKGROUND OF THE INVENTION

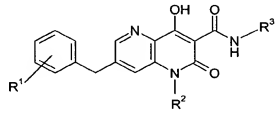
The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS"), a disease characterized by the destruction of the immune system, particularly of $CD4^+$ T-cells, with attendant susceptibility to opportunistic infections, and its precursor AIDS-related complex ("ARC"), a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss. HIV is a retrovirus; the conversion of its RNA to DNA is accomplished through the action of the enzyme reverse transcriptase. Compounds that inhibit the function of reverse transcriptase inhibit replication of HIV in infected cells. Such compounds are useful in the prevention or treatment of HIV infection in humans.

A required step in HIV replication in human T-cells is the insertion by virally-encoded integrase of proviral DNA into the host cell genome. Integration is believed to be mediated by integrase in a process involving assembly of a stable nucleoprotein complex with viral DNA sequences, cleavage of two nucleotides from the 3' termini of the linear proviral DNA and covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The repair synthesis of the resultant gap may be accomplished by cellular enzymes.

There is continued need to find new therapeutic agents to treat human diseases. HIV integrase is an attractive target for the discovery of new therapeutics due to its important role in viral infections, particularly HIV infections. Integrase inhibitors are disclosed in WO03/062204. The compounds of the present invention exhibit advantages over previously disclosed integrase inhibitors, for example increased potency, metabolic stability, increased therapeutic index, or other pharmaceutical properties.

SUMMARY OF THE INVENTION

The present invention features compounds that are HIV integrase inhibitors and therefore are useful in the inhibition of HIV replication, the prevention and/or treatment of infection by HIV, and in the treatment of AIDS and/or ARC. The present invention features compounds of formula (I):



(I)

wherein:

R^1 is one or more substituents independently selected from hydrogen, hydroxy, CN, $N(R^aR^b)$, C_{1-8}alkyl, C_{3-7} cycloalkyl, halogen and C_{1-8} alkoxy;

R^2 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, halogen, CN, NO_2, OR^a, $N(R^aR^b)$, $S(O)_mR^a$, SR^a, $OS(O)_mR^a$, $S(O)_mOR^a$, $OS(O)_mOR^a$, $N(R^a)S(O)_mR^b$, $S(O)_mN(R^aR^b)$, $N(R^a)S(O)_mN(R^aR^b)$, $OS(O)_mN(R^aR^b)$, $N(R^a)S(O)_mOR^b$, $C(O)R^a$, $OC(O)R^a$, $C(O)OR^a$, $OC(O)OR^a$, $N(R^a)C(O)R^b$, $C(O)N(R^aR^b)$, $N(R^a)C(O)N(R^aR^b)$, $OC(O)N(R^aR^b)$, $N(R^a)C(O)OR^b$, $C(NR^aR^b)=N(R^a)$, $N(R^a)C(NR^aR^b)=N(R^a)$, $C(SR^a)=N(R^b)$, $C(OR^a)=N(R^b)$, $N(R^a)C(SR^a)=N(R^b)$ and heterocycle optionally substituted with oxo or R^a;

or optionally when R^2 is C_{5-7} cycloalkyl, C_{6-14} aralkyl, C_{5-7} cycloalkenyl, C_{6-14} aryl or heterocycle R^2 may be fused to 5-7 membered carbocyclic or heterocyclic rings;

R^a and R^b are independently hydrogen, NO_2, OR^c, CN, $N(R^cR^d)$, $C(O)R^c$, $C(O)C(O)R^c$, $C(O)N(R^cR^d)$, $C(O)C(O)N(R^cR^d)$, $S(O)_mR^c$, SR^c, $S(O)_mN(R^cR^d)$, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, CN, NO_2, OR^c, $N(R^cR^d)$, $S(O)_mR^c$, SR^c, $OS(O)_mR^c$, $S(O)_mOR^c$, $OS(O)_mOR^c$, $N(R^c)S(O)_mR^d$, $S(O)_mN(R^cR^d)$, $N(R^c)S(O)_mN(R^cR^d)$, $OS(O)_mN(R^cR^d)$, $N(R^c)S(O)_mOR^d$, $C(O)R^c$, $OC(O)R^c$, $C(O)OR^c$, $OC(O)OR^c$, $N(R^c)C(O)R^d$, $C(O)N(R^cR^d)$, $N(R^c)C(O)N(R^cR^d)$, $OC(O)N(R^cR^d)$, $N(R^c)C(O)OR^d$, $C(NR^cR^d)=N(R^c)$, $C(SR^c)=N(R^d)$, $C(OR^c)=N(R^d)$ and heterocycle;

Optionally, R^a and R^b may be linked together through one or more ring carbon atoms and/or ring heteroatoms including N, O, $C(R^cR^d)$, C(O), $S(O)_m$, or S to form a saturated or unsaturated 3 to 8 membered carbocyclic or heterocyclic ring;

R^c and R^d are independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

Optionally, R^c and R^d may be linked together through one or more ring carbon atoms and/or ring heteroatoms including N, O, C(O) and $S(O)_m$, or S to form a saturated or unsaturated 3 to 8 membered carbocyclic or heterocyclic ring;

R^3 is hydrogen, hydroxy, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, $N(R^aR^b)$, or heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, halogen, oxo, CN, NO_2, OR^a, $N(R^aR^b)$, $S(O)_mR^a$, SR^a, $OS(O)_mR^a$, $S(O)_mOR^a$, $OS(O)_mOR^a$, $N(R^a)S(O)_mR^b$, $S(O)_mN(R^aR^b)$, $N(R^a)S(O)_mN(R^aR^b)$, $OS(O)_mN(R^aR^b)$, $N(R^a)S(O)_mOR^b$, $C(O)R^a$, $OC(O)R^a$, $C(O)OR^a$, $OC(O)OR^a$,

$N(R^a)C(O)R^b$, $C(O)N(R^aR^b)$, $N(R^a)C(O)N(R^aR^b)$, $OC(O)N(R^aR^b)$, $N(R^a)C(O)OR^b$, $C(NR^a)=N(R^b)$, $C(SR^a)=N(R^b)$, $C(OR^a)=N(R^b)$, $N(R^a)C(NR^aR^b)=N(R^a)$, $N(R^a)C(SR^a)=N(R^b)$, $N(R^a)C(OR^a)=N(R^b)$, and heterocycle optionally substituted by oxo or R^a;

m is 1 or 2;

or a pharmaceutically acceptable derivative thereof, provided that:

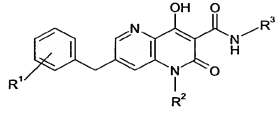
(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl , C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, or R^2 is C_{1-8} alkyl substituted with $S(O)_mR^a$ where R^a is C_{1-8} alkyl and m is 2, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes the compounds of Formula (I), useful in treating or preventing viral infections, particularly HIV infections, pharmaceutical compositions comprising compounds of Formula (I), and processes for preparing the compounds.

The present invention features compounds of formula (I):



(I)

wherein:

R^1 is one or more substituents independently selected from hydrogen, hydroxy, CN, $N(R^aR^b)$, C_{1-8}alkyl, C_{3-7} cycloalkyl, halogen and C_{1-8} alkoxy;

R^2 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, halogen, CN, NO_2, OR^a, $N(R^aR^b)$, $S(O)_mR^a$, SR^a, $OS(O)_mR^a$, $S(O)_mOR^a$, $OS(O)_mOR^a$, $N(R^a)S(O)_mR^b$, $S(O)_mN(R^aR^b)$, $N(R^a)S(O)_mN(R^aR^b)$, $OS(O)_mN(R^aR^b)$, $N(R^a)S(O)_mOR^b$, $C(O)R^a$, $OC(O)R^a$, $C(O)OR^a$, $OC(O)OR^a$, $N(R^a)C(O)R^b$, $C(O)N(R^aR^b)$, $N(R^a)C(O)N(R^aR^b)$, $OC(O)N(R^aR^b)$, $N(R^a)C(O)OR^b$, $C(NR^aR^b)=N(R^a)$, $N(R^a)C(NR^aR^b)=N(R^a)$, $C(SR^a)=N(R^b)$, $C(OR^a)=N(R^b)$, $N(R^a)C(SR^a)=N(R^b)$ and heterocycle optionally substituted with oxo or R^a;
or optionally when R^2 is C_{5-7} cycloalkyl, C_{6-14} aralkyl, C_{5-7} cycloalkenyl, C_{6-14} aryl or heterocycle R^2 may be fused to 5-7 membered carbocyclic or heterocyclic rings;

R^a and R^b are independently hydrogen, NO_2, OR^c, CN, $N(R^cR^d)$, $C(O)R^c$, $C(O)C(O)R^c$, $C(O)N(R^cR^d)$, $C(O)C(O)N(R^cR^d)$, $S(O)_mR^c$, SR^c, $S(O)_mN(R^cR^d)$, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, CN, NO_2, OR^c, $N(R^cR^d)$, $S(O)_mR^c$, SR^c, $OS(O)_mR^c$, $S(O)_mOR^c$, $OS(O)_mOR^c$, $N(R^c)S(O)_mR^d$, $S(O)_mN(R^cR^d)$, $N(R^c)S(O)_mN(R^cR^d)$, $OS(O)_mN(R^cR^d)$, $N(R^c)S(O)_mOR^d$, $C(O)R^c$, $OC(O)R^c$, $C(O)OR^c$, $OC(O)OR^c$, $N(R^c)C(O)R^d$, $C(O)N(R^cR^d)$, $N(R^c)C(O)N(R^cR^d)$, $OC(O)N(R^cR^d)$, $N(R^c)C(O)OR^d$, $C(NR^cR^d)=N(R^c)$, $C(SR^c)=N(R^d)$, $C(OR^c)=N(R^d)$ and heterocycle;

Optionally, R^a and R^b may be linked together through one or more ring carbon atoms and/or ring heteroatoms including N, O, $C(R^cR^d)$, C(O), $S(O)_m$, or S to form a saturated or unsaturated 3 to 8 membered carbocyclic or heterocyclic ring;

R^c and R^d are independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

Optionally, R^c and R^d may be linked together through one or more ring carbon atoms and/or ring heteroatoms including N, O, C(O) and $S(O)_m$ or S to form a saturated or unsaturated 3 to 8 membered carbocyclic or heterocyclic ring;

R^3 is hydrogen, hydroxy, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, $N(R^aR^b)$, or heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, halogen, oxo, CN, NO_2, OR^a, $N(R^aR^b)$, $S(O)_mR^a$, SR^a, $OS(O)_mR^a$, $S(O)_mOR^a$, $OS(O)_mOR^a$, $N(R^a)S(O)_mR^b$, $S(O)_mN(R^aR^b)$, $N(R^a)S(O)_mN(R^aR^b)$, $OS(O)_mN(R^aR^b)$, $N(R^a)S(O)_mOR^b$, $C(O)R^a$, $OC(O)R^a$, $C(O)OR^a$, $OC(O)OR^a$, $N(R^a)C(O)R^b$, $C(O)N(R^aR^b)$, $N(R^a)C(O)N(R^aR^b)$, $OC(O)N(R^aR^b)$, $N(R^a)C(O)OR^b$, $C(NR^a)=N(R^b)$, $C(SR^a)=N(R^b)$, $C(OR^a)=N(R^b)$, $N(R^a)C(NR^aR^b)=N(R^a)$, $N(R^a)C(SR^a)=N(R^b)$, $N(R^a)C(OR^a)=N(R^b)$, and heterocycle optionally substituted by oxo or R^a;

m is 1 or 2;

or a pharmaceutically acceptable derivative thereof, provided that:

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl, C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, or R^2 is C_{1-8} alkyl substituted with $S(O)_mR^a$ where R^a is C_{1-8} alkyl and m is 2, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl.

The term "alkyl", alone or in combination with any other term, refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like.

The term "cycloalkyl" refers to a saturated or partially saturated carbocyclic ring composed of 3-6 carbons in any chemically stable configuration. Examples of suitable carbocyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexenyl.

The term "alkenyl," alone or in combination with any other term, refers to a straight-chain or branched-chain alkyl group with at least one carbon-carbon double bond. Examples of alkenyl radicals include, but are not limited to, ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, hexenyl, hexadienyl and the like.

The term "alkynyl" refers to hydrocarbon groups of either a straight or branched configuration with one or more carbon-carbon triple bonds which may occur in any stable point along the chain, such as ethynyl, propynyl, butynyl, pentynyl, and the like.

The term "alkoxy" refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

The term "aryl" alone or in combination with any other term, refers to a carbocyclic aromatic moiety (such as phenyl or naphthyl) containing the specified number of carbon atoms, preferably from 6-14 carbon atoms, and more preferably from 6-10 carbon atoms. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl, indanyl, phenanthridinyl and the like. Unless otherwise indicated, the term "aryl" also includes each possible positional isomer of an aromatic

hydrocarbon radical, such as in 1-naphthyl, 2-naphthyl, 5-tetrahydronaphthyl, 6-tetrahydronaphthyl, 1-phenanthridinyl, 2-phenanthridinyl, 3-phenanthridinyl, 4-phenanthridinyl, 7-phenanthridinyl, 8-phenanthridinyl, 9-phenanthridinyl and 10-phenanthridinyl. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl, indanyl, phenanthridinyl and the like.

The term "aralkyl" refers to an alkyl group substituted by an aryl group. Examples of aralkyl groups include, but are not limited to, benzyl, phenethyl and the like.

The term "heterocycle," "heterocyclic," and "heterocyclyl" as used herein, refer to a 3- to 7- membered monocyclic heterocyclic ring or 8-to 11- membered bicyclic heterocyclic ring system any ring of which is either saturated, partially saturated or unsaturated, and which may be optionally benzofused if monocyclic. Each heterocycle consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen atom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any carbon or heteroatom, provided that the attachment results in the creation of a stable structure. Preferred heterocycles include 5-7 membered monocyclic heterocycles and 8-10 membered bicyclic heterocycles. When the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results. "Heteroaromatics" or "heteroaryl" are included within the heterocycles as defined above and generally refers to a heterocycle in which the ring system is an aromatic monocyclic or polycyclic ring radical containing five to twenty carbon atoms, preferably five to ten carbon atoms, in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, S and P. Preferred heteroaryl groups include 5-6 membered monocyclic

heteroaryls and 8 - 10 membered bicyclic heteroaryls. Also included within the scope of the term "heterocycle, "heterocyclic" or "heterocyclyl" is a group in which a non-aromatic heteroatom-containing ring is fused to one or more aromatic rings, such as in an indolinyl, chromanyl, phenanthridinyl or tetrahydro-quinolinyl, where the radical or point of attachment is on the non-aromatic heteroatom-containing ring. Unless otherwise indicated, the term "heterocycle, "heterocyclic" or "heterocyclyl" also included each possible positional isomer of a heterocyclic radical, such as in 1-indolinyl, 2-indolinyl, 3-indolinyl. Examples of heterocycles include imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, indazolyl, indazolinolyl, perhydropyridazyl, pyridazyl, pyridyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, pyranyl, pyrazolinyl, piperazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, oxazolyl, oxadiazolyl, benzoxazolyl, oxopiperidinyl, oxopyrrolidinyl, oxoazepinyl, azepinyl, isoxozolyl, isothiazolyl, furazanyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thiadiazoyl, dioxolyl, dioxinyl, oxathiolyl, benzodioxolyl, dithiolyl, thiophenyl, tetrahydrothiophenyl, sulfolanyl, dioxanyl, dioxolanyl, tetahydrofurodihydrofuranyl, tetrahydropyranodihydrofuranyl, dihydropyranyl, tetradyrofurofuranyl and tetrahydropyranofuranyl.

The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen, such as N(O) $\{N^+\text{-}O^-\}$ and sulfur such as S(O) and $S(O)_2$, and the quaternized form of any basic nitrogen.

A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure, i.e., the R and S configurations for each

asymmetric center. Therefore, racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereoisomers of the present compounds are expressly included within the scope of the invention. Although the specific compounds exemplified herein may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are also within the scope of this invention.

It will be apparent to one skilled in the art that certain compounds of this invention may exist in alternative tautomeric forms. All such tautomeric forms of the present compounds are within the scope of the invention. Unless otherwise indicated, the representation of either tautomer is meant to include the other.

The term "pharmaceutically effective amount" refers to an amount effective in treating a virus infection, for example an HIV infection, in a patient either as monotherapy or in combination with other agents. The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in a patient, or the improvement of an ascertainable measurement associated with a particular disorder, and may include the suppression of symptom recurrence in an asymptomatic patient such as a patient in whom a viral infection has become latent. The term "prophylactically effective amount" refers to an amount effective in preventing a virus infection, for example an HIV infection, or preventing the occurrence of symptoms of such an infection, in a patient. As used herein, the term "patient" refers to a mammal, including a human.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is

nontoxic when administered in doses sufficient to deliver a therapeutic amount of the antiviral agent.

The term "treatment" as used herein refers to the alleviation of symptoms of a particular disorder in a patient, or the improvement of an ascertainable measurement associated with a particular disorder, and may include the suppression of symptom recurrence in an asymptomatic patient such as a patient in whom a viral infection has become latent. Treatment includes prophylaxis which refers to preventing a disease or condition or preventing the occurrence of symptoms of such a disease or condition, in a patient. As used herein, the term "patient" refers to a mammal, including a human.

As used herein, the term "subject" refers to a patient, animal or a biological sample. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; preparations of an enzyme suitable for *in vitro* assay; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

Throughout this specification, the word "comprise" or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer or groups of integers but not the exclusion of any other integer or group of integers.

As used herein, the compounds according to the invention are defined to include pharmaceutically acceptable derivatives thereof. A "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of an ester, ether, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing directly or indirectly a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal, for example, by allowing an orally administered compound to be more readily absorbed into the blood, or which enhance delivery of the parent compound to a

biological compartment, for example, the brain or lymphatic system, relative to the parent species.

Pharmaceutically acceptable salts of the compounds according to the invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicyclic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g., magnesium), ammonium, NW_4^+ (wherein W is C_{1-4} alkyl) and other amine salts. Physiologically acceptable salts of a hydrogen atom or an amino group include salts or organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4}alkyl group). Preferred salts include sodium, calcium, potassium, magnesium, choline, meglumine, hydrochloride, and quaternary ammonium.

Other compounds of this invention may be prepared by one skilled in the art following the teachings of the specification coupled with knowledge in the art using reagents that are readily synthesized or commercially available.

Any reference to any of the above compounds also includes a reference to a pharmaceutically acceptable salt thereof.

Salts of the compounds of the present invention may be made by methods known to a person skilled in the art. For example, treatment of a compound of the present invention with an appropriate base or acid in an appropriate solvent will yield the corresponding salt.

Esters of the compounds of the present invention are independently selected from the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms, Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group.

Ethers of the compounds of the present invention include, but are not limited to methyl, ethyl, butyl and the like.

The present invention features a compound of formula (I) wherein:

R^1 is hydrogen or halogen;

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl optionally substituted with C_{3-7}cycloalkyl, OR^a, $N(R^aR^b)$, $C(O)R^a$, $C(O)N(R^aR^b)$, or heterocycle optionally substituted with oxo or R^a; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ or R^a; wherein m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$;

wherein R^a and R^b are independently hydrogen, OR^c, SR^c, C_{1-8}alkyl, C_{6-14}aryl or heterocycle, each of which each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, CN, NO_2, OR^c, $N(R^cR^d)$, $S(O)_mR^c$, SR^c, $OS(O)_mR^c$, $S(O)_mOR^c$, $OS(O)_mOR^c$, $N(R^c)S(O)_mR^d$, $S(O)_mN(R^cR^d)$, $N(R^c)S(O)_mN(R^cR^d)$, $OS(O)_mN(R^cR^d)$, $N(R^c)S(O)_mOR^d$, $C(O)R^c$, $OC(O)R^c$, $C(O)OR^c$, $OC(O)OR^c$, $N(R^c)C(O)R^d$, $C(O)N(R^cR^d)$, $N(R^c)C(O)N(R^cR^d)$, $OC(O)N(R^cR^d)$, $N(R^c)C(O)OR^d$, $C(NR^cR^d)=N(R^c)$, $C(SR^c)=N(R^d)$, $C(OR^c)=N(R^d)$ and heterocycle; wherein R^c is hydrogen , C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

R^c and R^d are independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

or a pharmaceutically acceptable derivative thereof provided that

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl , C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl.

The present invention features a compound of formula (I) wherein

R^1 is hydrogen or halogen;

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl optionally substituted with C_{3-7}cycloalkyl, OR^a, $N(R^aR^b)$, $C(O)R^a$, $C(O)N(R^aR^b)$, or heterocycle optionally substituted with oxo or R^a; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ or R^a; wherein m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$;

wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

wherein R^c is hydrogen, C_{1-8} alkyl or C_{6-14}aryl ;

or a pharmaceutically acceptable derivative thereof provided that

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl , C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl.

The present invention further features a compound of formula (I) wherein

R^1 is hydrogen or halogen;

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl substituted with C_{3-7}cycloalkyl, $C(O)R^a$ wherein R^a is heterocycle, or heterocycle optionally substituted with oxo; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ wherein R^a is C_{1-8}alkyl and m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a; wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

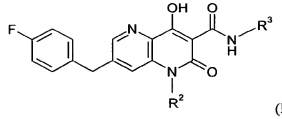
(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$ wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

wherein R^c is hydrogen, C_{1-8} alkyl or C_{6-14}aryl ;

or a pharmaceutically acceptable derivative thereof .

The present invention features a compound of formula (Ia)



(Ia)

wherein:

R^2 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, halogen, CN, NO_2, OR^a, $N(R^aR^b)$, $S(O)_mR^a$, SR^a, $OS(O)_mR^a$, $S(O)_mOR^a$, $OS(O)_mOR^a$, $N(R^a)S(O)_mR^b$, $S(O)_mN(R^aR^b)$, $N(R^a)S(O)_mN(R^aR^b)$, $OS(O)_mN(R^aR^b)$, $N(R^a)S(O)_mOR^b$, $C(O)R^a$, $OC(O)R^a$, $C(O)OR^a$, $OC(O)OR^a$, $N(R^a)C(O)R^b$, $C(O)N(R^aR^b)$, $N(R^a)C(O)N(R^aR^b)$, $OC(O)N(R^aR^b)$, $N(R^a)C(O)OR^b$, $C(NR^aR^b)=N(R^a)$, $N(R^a)C(NR^aR^b)=N(R^a)$, $C(SR^a)=N(R^b)$, $C(OR^a)=N(R^b)$, $N(R^a)C(SR^a)=N(R^b)$ and heterocycle optionally substituted with oxo or R^a;

or optionally when R^2 is C_{5-7} cycloalkyl, C_{6-14} aralkyl, C_{5-7} cycloalkenyl, C_{6-14} aryl or heterocycle R^2 may be fused to 5-7 membered carbocyclic or heterocyclic rings;

R^a and R^b are independently hydrogen, NO_2, OR^c, CN, $N(R^cR^d)$, $C(O)R^c$, $C(O)C(O)R^c$, $C(O)N(R^cR^d)$, $C(O)C(O)N(R^cR^d)$, $S(O)_mR^c$, SR^c, $S(O)_mN(R^cR^d)$, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, CN, NO_2, OR^c, $N(R^cR^d)$, $S(O)_mR^c$, SR^c, $OS(O)_mR^c$, $S(O)_mOR^c$,

$OS(O)_mOR^c$, $N(R^c)S(O)_mR^d$, $S(O)_mN(R^cR^d)$, $N(R^c)S(O)_mN(R^cR^d)$, $OS(O)_mN(R^cR^d)$, $N(R^c)S(O)_mOR^d$, $C(O)R^c$, $OC(O)R^c$, $C(O)OR^c$, $OC(O)OR^c$, $N(R^c)C(O)R^d$, $C(O)N(R^cR^d)$, $N(R^c)C(O)N(R^cR^d)$, $OC(O)N(R^cR^d)$, $N(R^c)C(O)OR^d$, $C(NR^cR^d)=N(R^c)$, $C(SR^c)=N(R^d)$, $C(OR^c)=N(R^d)$ and heterocycle;

Optionally, R^a and R^b may be linked together through one or more ring carbon atoms and/or ring heteroatoms including N, O, $C(R^cR^d)$, C(O), $S(O)_m$, or S to form a saturated or unsaturated 3 to 8 membered carbocyclic or heterocyclic ring;

R^c and R^d are independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

Optionally, R^c and R^d may be linked together through one or more ring carbon atoms and/or ring heteroatoms including N, O, C(O) and $S(O)_m$, or S to form a saturated or unsaturated 3 to 8 membered carbocyclic or heterocyclic ring;

R^3 is hydrogen, hydroxy, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, $N(R^aR^b)$, or heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, halogen, oxo, CN, NO_2, OR^a, $N(R^aR^b)$, $S(O)_mR^a$, SR^a, $OS(O)_mR^a$, $S(O)_mOR^a$, $OS(O)_mOR^a$, $N(R^a)S(O)_mR^b$, $S(O)_mN(R^aR^b)$, $N(R^a)S(O)_mN(R^aR^b)$, $OS(O)_mN(R^aR^b)$, $N(R^a)S(O)_mOR^b$, $C(O)R^a$, $OC(O)R^a$, $C(O)OR^a$, $OC(O)OR^a$, $N(R^a)C(O)R^b$, $C(O)N(R^aR^b)$, $N(R^a)C(O)N(R^aR^b)$, $OC(O)N(R^aR^b)$, $N(R^a)C(O)OR^b$, $C(NR^a)=N(R^b)$, $C(SR^a)=N(R^b)$, $C(OR^a)=N(R^b)$, $N(R^a)C(NR^aR^b)=N(R^a)$, $N(R^a)C(SR^a)=N(R^b)$, $N(R^a)C(OR^a)=N(R^b)$, and heterocycle optionally substituted by oxo or R^a;

m is 1 or 2;

or a pharmaceutically acceptable derivative thereof, provided that:

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl , C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, or R^2 is C_{1-8} alkyl substituted with $S(O)_mR^a$ where R^a is C_{1-8} alkyl and m is 2, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl.

The present invention features a compound of formula (Ia) wherein:

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl optionally substituted with C_{3-7}cycloalkyl, OR^a, $N(R^aR^b)$, $C(O)R^a$, $C(O)N(R^aR^b)$, or heterocycle optionally substituted with oxo or R^a; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ or R^a; wherein m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$;

wherein R^a and R^b are independently hydrogen, OR^c, SR^c, C_{1-8}alkyl, C_{6-14}aryl or heterocycle, each of which each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, CN, NO_2, OR^c, $N(R^cR^d)$, $S(O)_mR^c$, SR^c, $OS(O)_mR^c$, $S(O)_mOR^c$, $OS(O)_mOR^c$, $N(R^c)S(O)_mR^d$, $S(O)_mN(R^cR^d)$, $N(R^c)S(O)_mN(R^cR^d)$, $OS(O)_mN(R^cR^d)$, $N(R^c)S(O)_mOR^d$, $C(O)R^c$, $OC(O)R^c$, $C(O)OR^c$, $OC(O)OR^c$, $N(R^c)C(O)R^d$,

$C(O)N(R^cR^d)$, $N(R^c)C(O)N(R^cR^d)$, $OC(O)N(R^cR^d)$, $N(R^c)C(O)OR^d$, $C(NR^cR^d)=N(R^c)$, $C(SR^c)=N(R^d)$, $C(OR^c)=N(R^d)$ and heterocycle;

wherein R^c is hydrogen , C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

R^c and R^d are independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

or a pharmaceutically acceptable derivative thereof provided that

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl , C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl.

The present invention features a compound of formula (Ia) wherein:

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl optionally substituted with C_{3-7}cycloalkyl, OR^a, $N(R^aR^b)$, $C(O)R^a$, $C(O)N(R^aR^b)$, or heterocycle optionally substituted with oxo or R^a; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ or R^a; wherein m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$;

wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

wherein R^c is hydrogen, C_{1-8}alkyl or C_{6-14}aryl ;

or a pharmaceutically acceptable derivative thereof provided that

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8}alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8}alkyl , C_{1-8}alkyl substituted with $C(O)R^a$ where R^a is C_{1-8}alkyl, then R^3 cannot be C_{1-8}alkyl or C_{1-8}alkyl substituted with OR^a where R^a is C_{1-8}alkyl.

The present invention further features a compound of formula (Ia) wherein:

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl substituted with C_{3-7}cycloalkyl, $C(O)R^a$ wherein R^a is heterocycle, or heterocycle optionally substituted with oxo; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ wherein R^a is C_{1-8}alkyl and m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a; wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$ wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

wherein R^c is hydrogen, C_{1-8} alkyl or C_{6-14}aryl ;

or a pharmaceutically acceptable derivative thereof.

The present invention features a compound selected from the group consisting of:

Ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-(4-fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-benzyl-*N*-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Methyl 7-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-*N*,4-dihydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

N-Cyclopropyl-7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-morpholin-4-ylethyl)-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-4-hydroxy-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-*N*-(2-methylpropyl)-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cycloheptyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclopentyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclobutyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-*N*-[2-(methyloxy)ethyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-2-oxo-*N*-(2-phenylethyl)-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-2-oxo-*N*-(1-phenylethyl)-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-(Cyclohexylmethyl)-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-(2-Furanylmethyl)-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclohexyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-2-oxo-7-(phenylmethyl)-*N*-(2-thienylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclopropyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclobutyl-7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclopropyl-7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-*N*-(2-furanylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[3-(2-oxo-1-pyrrolidinyl)propyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[2-(1-pyrrolidinyl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

(±)-7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(tetrahydro-2-furnylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[2-(1-piperidinyl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(4-pyridinylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(2-pyridinylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(3-pyridinylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-*N*-(hexahydro-1*H*-azepin-1-yl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-*N*-[2-(4-morpholinyl)ethyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(5-Fluoro-2-pyridinyl)methyl]-4-hydroxy-*N*-[3-(4-morpholinyl)propyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[2-(2-pyridinyl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

Benzyl-*N*-cyclobutyl-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-*N*-cyclopropyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-*N*-cyclobutyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-*N*-(2-furylmethyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-4-hydroxy-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-*N*-cyclopropyl-4-hydroxy-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-1-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-1-(cyclopropylmethyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-*N*-cyclobutyl-1-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide ;

Ethyl 7-benzyl-4-hydroxy-1-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-*N*-cyclobutyl-4-hydroxy-1-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-*N*-(3-morpholin-4-ylpropyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(2-pyrrolidin-1-ylethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-4-hydroxy-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-*N*-cyclobutyl-4-hydroxy-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-(4-fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(pyridin-3-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-*N*-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

N-(2-Furanylmethyl)-4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-*N*-[2-(methyloxy)ethyl]-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclobutyl-4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

1-[(4-Aminophenyl)methyl]-*N*-cyclobutyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

and pharmaceutically acceptable salts thereof.

The present invention features a compound selected from the group consisting of:

7-(4-fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclopropyl-7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-morpholin-4-ylethyl)-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-*N*-[2-(methyloxy)ethyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[3-(2-oxo-1-pyrrolidinyl)propyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-*N*-[2-(4-morpholinyl)ethyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(5-Fluoro-2-pyridinyl)methyl]-4-hydroxy-*N*-[3-(4-morpholinyl)propyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-Benzyl-1-(cyclopropylmethyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
and pharmaceutically acceptable salts thereof.

The present invention features a compound selected from the group consisting of examples numbers 2, 9, 10, 12, 17, 28, 36, 37, 45, 49, 50, 54, 62, 64, 83, 84, 85, 86, 89, 91, 93, 94, 95, 96, 97, 98, 99, 101, 102, 104, 105, 106, 107 and pharmaceutically acceptable salts thereof. The present invention further features a compound selected from the group consisting of examples numbers 12, 36, 37, 49, 84, 89, 91, 93, 95, 96, 101 and pharmaceutically acceptable salts thereof.

Compounds of the present invention are useful as integrase inhibitors. One aspect of the instant invention relates to methods of treating or preventing viral infection, for example an HIV infection, in a biological sample comprising contacting the biological sample with compounds of formula (I) or (Ia) or pharmaceutically acceptable derivatives thereof. Another aspect of the instant invention relates to methods of treating or preventing viral infection, for example, an HIV infection, in a patient comprising administering to the patient a therapeutically effective amount of compounds of formula (I) or (Ia) or pharmaceutically acceptable derivatives thereof.

The compounds according to the invention are particularly suited to the treatment or prophylaxis of HIV infections and associated conditions. Reference herein to treatment extends to prophylaxis as well as the treatment of established infections, symptoms, and associated clinical conditions such as AIDS related complex (ARC), Kaposi's sarcoma, and AIDS dementia.

The compounds of the present invention exhibit advantages over previously disclosed integrase inhibitors, for example increased potency, metabolic stability, increased therapeutic index, or other pharmaceutical properties.

According to one embodiment of the invention, compounds of formula (I) or (Ia) or salts thereof may be formulated into compositions. In a preferred embodiment, the composition is a pharmaceutical composition, which comprises a compound of formula (I) or (Ia) and pharmaceutically acceptable carrier, adjuvant or vehicle. In one embodiment, the composition comprises an amount of a compound of the present invention effective to treat or prevent viral infection, for example an HIV infection, in a biological sample or in a patient. In another embodiment, compounds of this invention and pharmaceutical compositions thereof, which comprise an amount of a compound of the present innovation effective to inhibit viral replication or to treat or prevent a viral infection or disease or disorder, for example an HIV infection, and a pharmaceutically acceptable carrier, adjuvant or vehicle, may be formulated for administration to a patient, for example, for oral administration.

The present invention features compounds according to the invention for use in medical therapy, for example for the treatment or prophylaxis of a viral infection, for example an HIV infection and associated conditions. The compounds according to the invention are especially useful for the treatment of AIDS and related clinical conditions such as AIDS related complex (ARC), progressive generalized lymphadenopathy (PGL), Kaposi's sarcoma, thromobocytopenic purpura, AIDS-related neurological conditions such as AIDS dementia complex, multiple sclerosis or tropical paraperesis, anti-HIV antibody-positive and HIV-positive conditions, including such conditions in asymptomatic patients.

According to another aspect, the present invention provides a method for the treatment or prevention of the symptoms or effects of a viral infection in an infected patient, for example, a mammal including a human, which comprises administering to said patient a pharmaceutically effective amount of a compound according to the invention. According to one aspect of the invention, the viral infection is a retroviral infection, in particular an HIV infection.

The present invention further includes the use of a compound according to the invention in the manufacture of a medicament for administration to a subject for the treatment of a viral infection, in particular and HIV infection.

The compounds according to the invention may also be used in adjuvant therapy in the treatment of HIV infections or HIV-associated symptoms or effects, for example Kaposi's sarcoma.

The present invention further provides a method for the treatment of a clinical condition in a patient, for example, a mammal including a human which clinical condition includes those which have been discussed hereinbefore, which comprises treating said patient with a pharmaceutically effective amount of a compound according to the invention. The present invention also includes a method for the treatment or prophylaxis of any of the aforementioned diseases or conditions.

Reference herein to treatment extends to prophylaxis as well as the treatment of established conditions, disorders and infections, symptoms thereof, and associated. The above compounds according to the invention and their pharmaceutically acceptable derivatives may be employed in combination with other therapeutic agents for the treatment of the above infections or conditions. Combination therapies according to the present invention comprise the administration of a compound of the present invention or a pharmaceutically acceptable derivative thereof and another pharmaceutically active agent. The active ingredient(s) and pharmaceutically active agents may be administered simultaneously (i.e., concurrently) in either the same or different pharmaceutical compositions or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings

of administration will be selected in order to achieve the desired combined therapeutic effect.

Examples of such therapeutic agents include, but are not limited to, agents that are effective for the treatment of viral infections or associated conditions. Among these agents are (1-alpha, 2-beta, 3-alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514, lobucavir]; 9-[(2R,3R,4S)-3,4-bis(hydroxy methyl)2-oxetanosyl]adenine (oxetanocin-G); acyclic nucleosides, for example acyclovir, valaciclovir, famciclovir, ganciclovir, and penciclovir; acyclic nucleoside phosphonates, for example (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl) cytosine (HPMPC), [[[2-(6-amino-9H-purin-9-yl)ethoxy] methyl]phosphinylidene] bis(oxymethylene)-2,2-dimethyl propanoic acid (bis-POM PMEA, adefovir dipivoxil), [[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl] phosphonic acid (tenofovir), and (R)-[[2-(6-Amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid bis-(isopropoxycarbonyloxymethyl)ester (bis-POC-PMPA); ribonucleotide reductase inhibitors, for example 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl) thiocarbonohydrazone and hydroxyurea; nucleoside reverse transcriptase inhibitors, for example 3'-azido-3'-deoxythymidine (AZT, zidovudine), 2',3'-dideoxycytidine (ddC, zalcitabine), 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine (ddI, didanosine), 2',3'-didehydrothymidine (d4T, stavudine), (-)-beta-D-2,6-diaminopurine dioxolane (DAPD), 3'-azido-2',3'-dideoxythymidine-5'-H-phosphophonate (phosphonovir), 2'-deoxy-5-iodo-uridine (idoxuridine), (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine), cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclo-propylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), ABT-606 (2HM-H2G) and ribavirin; protease inhibitors, for example indinavir, ritonavir, nelfinavir, amprenavir, saquinavir, fosamprenavir, (R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-(isoquinolin-5-yloxyacetyl)amino-3-

methylthio-propanoyl]amino-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide (KNI-272), 4R-(4alpha, 5alpha,6beta)]-1,3-bis[(3-aminophenyl)methyl]hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-one dimethanesulfonate (mozenavir), 3-[1-[3-[2-(5-trifluoromethylpyridinyl)-sulfonylamino]phenyl]propyl]-4- hydroxy-6alpha-phenethyl-6beta-propyl-5,6-dihydro-2-pyranone (tipranavir), N'-[2(S)-Hydroxy-3(S)-[N-(methoxycarbonyl)-l-tert-leucylamino]-4-phenylbutyl-N ^{alpha}-(methoxycarbonyl)-N'-[4-(2-pyridyl)benzyl]-L- tert-leucylhydrazide (BMS-232632), 3-(2(S)-Hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-phenylbutanoyl)-5,5-dimethyl-N-(2-methylbenzyl)thiazolidine-4(R)-carboxamide (AG-1776), N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenyl-methyl-4(S)-hydroxy-5-(1-(1-(4-benzo[b]furanylmethyl)-2(S)-N'-(tert-butyl carboxamido)piperazinyl)pentanamide (MK-944A); interferons such as α-interferon; renal excretion inhibitors such as probenecid; nucleoside transport inhibitors such as dipyridamole, pentoxifylline, N-acetylcysteine (NAC), Procysteine, α-trichosanthin, phosphonoformic acid; as well as immunomodulators such as interleukin II or thymosin, granulocyte macrophage colony stimulating factors, erythropoetin, soluble CD_4 and genetically engineered derivatives thereof; non-nucleoside reverse transcriptase inhibitors (NNRTIs), for example nevirapine (BI-RG-587), alpha-((2-acetyl-5-methylphenyl)amino)-2,6-dichloro-benzeneacetamide (loviride), 1-[3-(isopropyl amino)-2-pyridyl]-4-[5-(methanesulfonamido)-1H-indol-2-ylcarbonyl]piperazine monomethanesulfonate (delavirdine), (10R, 11S, 12S)-12-Hydroxy-6, 6, 10, 11-tetramethyl-4-propyl-11,12-dihydro-2H, 6H, 10H-benzo(1, 2-b:3, 4-b':5, 6-b'')tripyran-2-one ((+) calanolide A), (4S)-6-Chloro-4-[1E)-cyclopropyl ethenyl)-3,4- dihydro-4-(trifluoromethyl)-2(1H)-quinazolinone (DPC-083), (S)-6-chloro-4-(cyclopropyl ethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one (efavirenz, DMP 266), 1-(ethoxy methyl)-5-(1-methylethyl)-6-(phenylmethyl)-2,4(1H,3H)-pyrimidinedione (MKC-442), and 5-(3,5-dichloro phenyl)thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbamate (capravirine); glycoprotein 120 antagonists, for example PRO-2000, PRO-542 and 1,4-bis[3-[(2, 4-

dichlorophenyl)carbonyl amino]-2-oxo-5,8-disodiumsulfanyl]naphthalyl-2, 5-dimethoxyphenyl-1, 4-dihydrazone (FP-21399); cytokine antagonists, for example reticulose (Product-R), 1,1'-azobis-formamide (ADA), 1,11-(1,4-phenylenebis (methylene))bis-1,4,8,11-tetraazacyclotetradecane octahydrochloride (AMD-3100); integrase inhibitors; and fusion inhibitors, for example T-20 and T-1249.

The present invention further includes the use of a compound according to the invention in the manufacture of a medicament for simultaneous or sequential administration with at least another therapeutic agent, such as those defined hereinbefore.

Compounds of the present invention may be administered with an agent known to inhibit or reduce the metabolism of compounds, for example ritonavir. Accordingly, the present invention features a method for the treatment or prophylaxis of a disease as hereinbefore described by administration of a compound of the present invention in combination with a metabolic inhibitor. Such combination may be administered simultaneously or sequentially.

In general a suitable dose for each of the above-mentioned conditions will be in the range of 0.01 to 250 mg per kilogram body weight of the recipient (e.g. a human) per day, preferably in the range of 0.1 to 100 mg per kilogram body weight per day and most preferably in the range 0.5 to 30 mg per kilogram body weight per day and particularly in the range 1.0 to 20 mg per kilogram body weight per day. Unless otherwise indicated, all weights of active ingredient are calculated as the parent compound of formula (I) or (Ia); for salts or esters thereof, the weights would be increased proportionally. The desired dose may be presented as one, two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. In some cases the desired dose may be given on alternative days. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1000 mg or 50 to 500 mg, preferably 20 to 500 mg, and most preferably 50 to 400 mg of active ingredient per unit dosage form.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. The compositions of the present invention comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof and optionally other therapeutic agents. Each carrier must be acceptable in the sense of being compatible with the other ingredients of the composition and not injurious to the patient.

Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, and intravitreal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier, which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

The present invention further includes a pharmaceutical composition as hereinbefore defined wherein a compound of the present invention or a pharmaceutically acceptable derivative thereof and another therapeutic agent are presented separately from one another as a kit of parts.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 25%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport or iontophoresis as generally described in Pharmaceutical Research 3(6), 318 (1986).

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Pharmaceutical compositions suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray. Pharmaceutical compositions may contain in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical compositions for rectal administration may be presented as a suppository with a suitable carrier comprising, for example, cocoa butter or a salicylate or other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

Pharmaceutical compositions suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the pharmaceutical composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The pharmaceutical compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Unit dosage pharmaceutical compositions include those containing a daily dose or daily subdose of the active ingredients, as hereinbefore recited, or an appropriate fraction thereof.

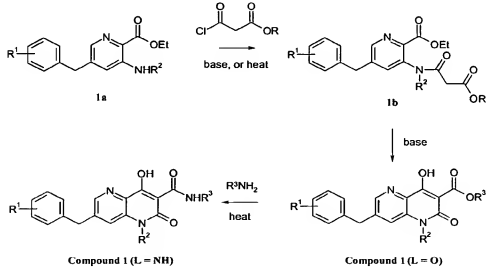
It should be understood that in addition to the ingredients particularly mentioned above the pharmaceutical compositions of this invention may include other agents conventional in the art having regard to the type of pharmaceutical composition in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

The compounds of the present invention may be prepared according to the following reactions schemes and examples, or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these

reactions, it is also possible to make use of variants which are known to those of ordinary skill in the art.

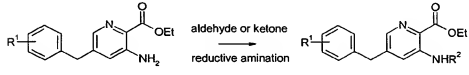
The compounds of the present invention are readily prepared by methods outlined in Schemes 1-3 or by methods known to one skilled in the art. Compounds of formula I where L = NH may be prepared by treating compounds of formula I where L = O with amines (R^3NH_2). These and other methods for the conversion of carboxylic esters and acid derivatives to amides are well known to those skilled in the art. For examples, see: March, J., Advanced Organic Chemistry, 4th Edition; John Wiley & Sons, 1992, pp 419-424. Compounds of formula I (L = O) are prepared by treating 3-oxopropanoyl derivatives 1b with base (e.g. NaOMe or NaOEt) in protic solvents such as MeOH or EtOH. Oxopropanoyl derivatives 1b may be prepared by reacting amines 1a with malonylchloride derivatives in the presence of base. Alternatively, compounds 1b are prepared by heating a solution of amine 1a with a malonylchloride derivatives in a nonprotic solvent.

SCHEME 1



Amines 2b may be prepared by reductive amination of amines 2a with aldehydes and ketones as outlined in Scheme 2. For examples, of reductive amination reactions, see: March, J., Advanced Organic Chemistry, 4th Edition; John Wiley & Sons, 1992, pp 898-900.

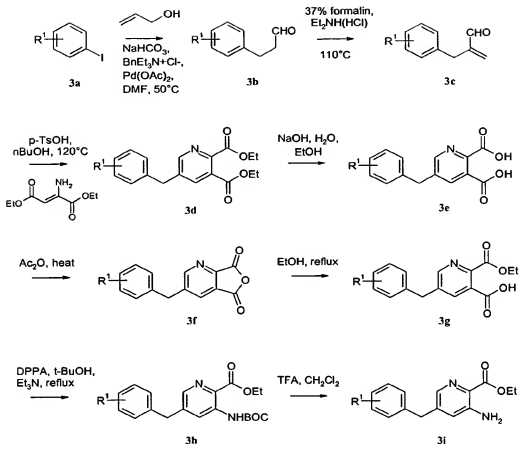
SCHEME 2



2a 2b

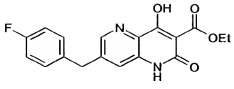
Amines 3i are readily prepared by methods outlined in Scheme 3. Heck reaction of aryl iodides 3a with allyl alcohol generates 3-arylproponals 3b. For examples of Heck reactions in the preparation of 3b, see: March, J., Advanced Organic Chemistry, 4th Edition; John Wiley & Sons, 1992, pp 717-718. Treatment of 3b with formaldehyde in the presence of diethylamine hydrochloride affords requisite 2-benzylpropenals 3c. Reaction of 3c with diethyl 2-aminofumarate provides a pyridine diethyl ester 3d which may be hydrolyzed under basic conditions (e.g. NaOH) to the corresponding pyridine dicarboxylic acid 3e. For synthesis of diethyl 2-aminofumarate, see: Isobe, K.; Mohiri, C.; Sano, H.; Mohri, K.; Enomoto, H., Chem. Pharm. Bull., Vol. 37, 1989, pp3236-3238. Treatment of 3e with acetic anhydride yields the corresponding cyclic anhydride 3f which is treated with EtOH at reflux to generate the pyridine carboxylic acid monoester 3g. Curtius rearrangement of 3g in the presence of t-BuOH yields the BOC-protected 3-aminopyridine derivative 3h which may be deprotected with TFA to afford the desired 3-aminopyridine compound 3i. For an example of a Curtius rearrangement of this type, see: Feiser, M., Reagents for Organic Synthesis, Vol. 11; John Wiley & Sons, 1984, p 222.

SCHEME 3

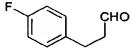


The following examples are intended for illustratation only and are not intended to limit the scope of the invention in any way.

Example 1: Ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate

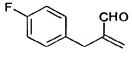


Step 1: Synthesis of 3-(4-fluorophenyl)propanal



To a mixture of 1-fluoro-4-iodobenzene (300 g, 1.35 mol), benzyltriethylammonium chloride (300 g, 1.35 mol), $NaHCO_3$ (283 g, 3.4 mol) and allyl alcohol (138 mL, 2.0 mol) in DMF (300 mL) was added palladium acetate (3.0 g, 13.5 mmol). The mixture was heated at 50 °C for 5 h with stirring. Water (1 L) and Et_2O (1 L) were added at rt. After filtration through Celite, the filtrate was extracted with Et_2O. The extracts were washed with H_2O and brine, then dried and concentrated to yield the product: ^1H NMR ($CDCl_3$) δ 9.81 (1H, s), 7.16 (2H, m), 6.97 (2H, m), 2.93 (2H, t, J = 7.5 Hz), 2.77 (2H, t, J = 7.5 Hz).

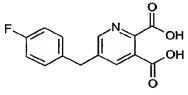
Step 2: Synthesis of 2-(4-fluorobenzyl)propenal



A mixture of 3-(4-fluorophenyl)propanal (205 g, 1.3 mol), diethylamine hydrochloride (148 g, 1.3 mol) and 37% formalin (ca. 1.2 eq.) was heated at 110 °C for 2h. Water (600 mL) was added and the mixture was extracted with EtOAc. The extract was washed with H_2O and brine, then dried and concentrated to afford the

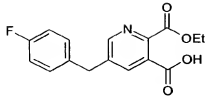
product: ^{1}H NMR ($CDCl_3$) δ 9.59 (1H, s), 7.13 (2H, m), 6.98 (2H, m), 6.10 (2H, m), 3.55 (2H, s).

Steps 3 and 4: Synthesis of 5-(4-fluorobenzyl)-2,3-pyridinedicarboxylic acid



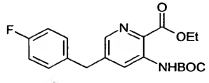
To a solution of diethyl 2-aminofumarate (153 g, 0.81 mol) and p-TsOH·H_2O (1.5 g, 8.1 mmol) in n-BuOH (325 mL) was added 2-(4-fluorobenzyl)propenal (162 g, 0.98 mol) dropwise at 120°C. The mixture was stirred for 17 h at 120°C and at rt for ca. 24h. The mixture was filtered and concentrated under vacuum to yield the crude diethyl 5-(4-fluorobenzyl)-2,3-pyridinedicarboxylate. This material was dissolved in EtOH (400 mL) and an ice-cold solution of NaOH (88 g, 2.2 mol) in water (300 mL) was added. The mixture was stirred for 2 h at rt. After removal of EtOH in vacuo, water (400 mL) and 6N HCl (200 mL) were added and the mixture was extracted with EtOAc. The EtOAc layer was washed with water and the combined aqueous layers adjusted to pH 2 with 6N HCl (175 mL). The mixture was stirred for 1 h at ice-bath temperature and the product was collected by filtration: ^{1}H NMR (d_6-DMSO) δ 8.64 (1H, d, J = 2 Hz), 8.01 (1H, d, J = 2 Hz), 7.32 (2H, dd, J ~ 9, 6Hz), 7.12 (2H, t, J ~ 9 Hz), 4.05 (2H, s); ES^+ MS: 276 ($M+H^+$, 100).

Steps 5 and 6: Synthesis of 5-(4-fluorobenzyl)-2,3-pyridinedicarboxylic acid 2-ethyl ester



A mixture of 5-(4-fluorobenzyl)-2,3-pyridinedicarboxylic acid (25.3 g, 92 mmol) and Ac_2O (200 mL) was stirred for 3 h at 120°C. The reaction mixture was concentrated in vacuo, dissolved in toluene (200 mL) and re-concentrated in vacuo again to give 5-(4-fluorobenzyl)-2,3-pyridinedicarboxylic anhydride. This material was dissolved in EtOH (200 mL) and the mixture was heated at reflux for 3 h and then stored at rt overnight. The reaction mixture was concentrated in vacuo, dissolved in toluene and concentrated again to afford the product as the major isomer. This material contained ca. 30% of the corresponding 3-ethyl ester 2-carboxylic acid isomer. Major isomer: ^{1}H NMR (d_6-DMSO) δ 13.5 (1H, br), 8.67 (1H, d, J = 2 Hz), 8.06 (1H, d, J = 2 Hz), 7.31 (2H, dd, J ~ 9, 6Hz), 7.11 (2H, t, J ~ 9 Hz), 4.25 (2H, q, J = 7 Hz), 1.24 (3H, t, J = 7 Hz); ES$^+$MS: 304 ($M+H^+$, 80), 326 ($M+Na^+$, 30).

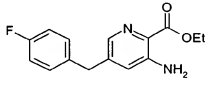
Step 7: Synthesis of ethyl 5-(4-fluorobenzyl)-3-[(tert-butoxy)carbonyl]amino-2-pyridinecarboxylate



A solution of 5-(4-fluorobenzyl)-2,3-pyridinedicarboxylic acid 2-ethyl ester (28 g, 92 mmol), diphenylphosphoryl azide (29.7 mL, 138 mmol) and Et_3N (38.5 mL, 276 mmol) in t-BuOH (250 mL) was heated at reflux for 5 h and stored at rt for 3 d. After removal of solvent in vacuo, EtOAc was added and the mixture was washed with

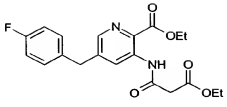
NH_4Cl solution, $NaHCO_3$ solution and brine, and then dried and concentrated. The crude material was purified by column chromatography on silica gel eluting with 30% EtOAc/hexanes to afford the product as the major isomer. This material contained ca. 30% of the corresponding 3-ethyl ester 2-(tert-butoxy)carbonylamino isomer. Major isomer: ^1H NMR (d_6-DMSO) δ 9.96 (1H, s), 8.30 (1H, d, J = 2 Hz), 8.24 (1H, d, J = 2 Hz), 7.27 (2H, m), 7.11 (2H, m), 4.28 (2H, q, J = 7 Hz), 4.01 (2H, s), 1.43 (9H, s), 1.28 (3H, t, J = 7 Hz); AP^+ MS: 375 ($M+H^+$, 100).

Step 8: Synthesis of ethyl 3-amino-5-(4-fluorobenzyl)-2-pyridinecarboxylate



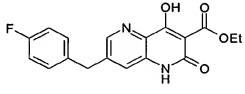
A solution of 5-(4-fluorobenzyl)-3-[(tert-butoxy)carbonyl]amino-2-pyridinecarboxylate (29 g, 77 mmol) in CH_2Cl_2 (200 mL) and trifluoroacetic acid (60 mL) was stirred at rt overnight. The solvent was removed in vacuo and the crude material was dissolved in EtOAc and washed with $NaHCO_3$ solution and brine. The organic layer was dried, concentrated and chromatographed on silica gel eluting with 20-60% EtOAc/hexanes to yield the product as a light yellow solid: ^1H NMR (d_6-DMSO) δ 7.76 (1H, d, J = 1.7 Hz), 7.25 (2H, m), 7.15 (2H, t, J = 9 Hz), 6.92 (1H, d, J = 1.7 Hz), 6.62 (2H, br s), 4.23 (2H, q, J = 7 Hz), 3.87 (2H, s), 1.26 (3H, t, J = 7 Hz); AP^+ MS: 275 ($M+H^+$, 100); HRMS calcd for $C_{15}H_{15}FN_2O_2+H^+$: 275.1196. Found: 275.1206.

Step 9: Synthesis of ethyl 3-[(3-ethoxy-3-oxopropanoyl)amino]-5-(4-fluorobenzyl)pyridine-2-carboxylate



Ethyl 3-chloro-3-oxopropionate (1.32 g, 8.75 mmol) was added to a solution of ethyl 3-amino-5-(4-fluorobenzyl)-2-pyridinecarboxylate (2 g, 7.29 mmol) in DCE (20 mL) and the solution was heated at reflux for 1 h. The solvent was removed in vacuo and silica gel chromatography eluting with 0-5% $MeOH/CH_2Cl_2$ provide the product as an amber oil: ^1H NMR ($CDCl_3$) δ 8.96 (1H, br s), 8.32 (1H, d, J = 1.8 Hz), 7.17 (2H, dd, J ~ 9, 6 Hz), 7.00 (2H, t, J ~ 9 Hz), 4.53 (2H, t, J = 7 Hz), 4.29 (2H, t, J = 7 Hz), 4.02 (2H, s), 3.54 (2H, s), 1.48 (3H, t, J = 7 Hz), 1.33 (3H, t, J = 7 Hz).

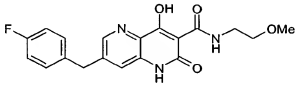
Step 10: Synthesis of ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate



A 2M solution of NaOEt in EtOH (5.87 mL, 11.74 mmol) was added to a solution of ethyl 3-[(3-ethoxy-3-oxopropanoyl)amino]-5-(4-fluorobenzyl)pyridine-2-carboxylate (2.28 g, 5.87 mmol) in EtOH (23 mL) and the mixture was stirred at rt for 1 h. The mixture was neutralized with conc. HCl and concentrated in vacuo. Trituration of the resulting material with a mixture of EtOH and 1:1 brine/water followed by filtration afforded the product as a beige solid: ^1H NMR (d_6-DMSO) δ 11.54 (1H, br s), 8.54 (1H, d, J = 1.4 Hz), 7.44 (1H, s), 7.32 (2H, dd, J = 8, 6 Hz), 7.17 (2H, t, J ~ 9 Hz),

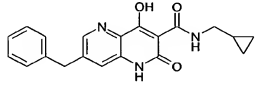
4.23 (2H, q, J = 7 Hz), 4.12 (2H, s), 1.26 (3H, t, J = 7 Hz); HRMS calcd for $C_{18}H_{15}FN_2O_4+H^+$: 343.1094. Found: 343.1088.

Example 2: 7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide

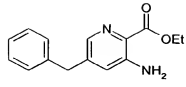


A mixture of ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate (35 mg, 0.102 mmol) and 2-methoxyethylamine (384 mg, 5.11 mmol) was heated at 120°C in a sealed tube for 18 h. The material was triturated with hot EtOH and filtered to give the product as a white solid: ^{1}H NMR (d_6-DMSO) δ 8.37 (1H, br), 7.39 (1H, br), 7.31 (2H, br t, J ~ 8 Hz), 7.15 (2H, br t, J ~ 9 Hz), 4.07 (2H, br), 3.47 (4H, br), 3.33 (3H, s); HRMS calcd for $C_{19}H_{18}FN_3O_4+H^+$: 372.1360. Found: 372.1372.

Example 3: 7-Benzyl-*N*-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide

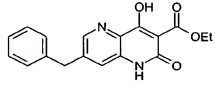


Steps 1-8. Synthesis of ethyl 3-amino-5-benzylpyridine-2-carboxylate



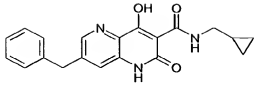
This compound was prepared from 3-phenylpropanal and diethyl 2-aminofumarate employing methods similar to those described in Example 1, Steps 2-8. The product was obtained as a beige solid: ^{1}H NMR (d_6-DMSO) δ 7.77 (1H, d, J = 1.6 Hz), 7.30 (2H, d, J = 8 Hz), 7.21 (3H, m), 6.94 (1H, d, J = 1.6 Hz), 6.62 (2H, br s), 4.23 (2H, q, J = 7 Hz), 3.97 (2H, s), 1.26 (3H, t, J = 7 Hz); HRMS calcd for $C_{15}H_{16}N_2O_2+H^+$: 257.1290. Found: 257.1286.

Steps 9-10: Ethyl 7-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate



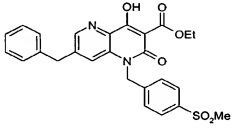
This compound was prepared from ethyl 3-amino-5-benzylpyridine-2-carboxylate and ethyl 3-chloro-3-oxopropionate employing methods similar to those described in Example 1, Steps 9-10. The product was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 10.72 (1H, br s), 8.24 (1H, br s), 7.36-7.23 (6H, m), 4.14 (2H, q, J = 7 Hz), 4.06 (2H, s), 1.22 (3H, t, J = 7 Hz); ES$^+$ MS: 325 ($M+H^+$, 75), 347 ($M+Na^+$, 26); Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 53.61; H, 3.99; N, 6.94. Found: C, 53.40; H, 3.92; N, 6.92.

Synthesis of 7-Benzyl-*N*-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide

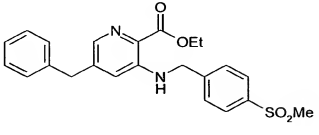


Ethyl 7-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate was treated with cyclopropylmethyl amine in a manner similar to that described in Example 2. The product was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 11.85 (1H, br), 10.85 (1H, br), 10.11 (1H, br),8.20 (1H, br m), 7.39-7.25 (6H, br m), 4.01 (2H, br s), 3.33-3.13 (2H, br m), 1.20-0.90 (1H, m), 0.44 (2H, m), 0.19 (2H, m); HRMS calcd for $C_{20}H_{19}N_3O_3+H^+$: 350.1505. Found: 350.1517.

Example 4: Ethyl 7-benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-

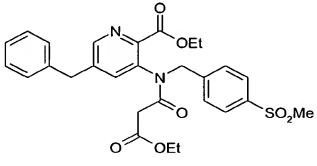


Step 1: Synthesis of ethyl 5-benzyl-3-{[4-(methylsulfonyl)benzyl]amino}pyridine-2-carboxylate



A solution of 1M BH_3•SMe_2 in CH_2Cl_2 (7 mL, 7 mmol) was added dropwise to a solution of ethyl 3-amino-5-benzylpyridine-2-carboxylate (600 mg, 2.34 mmol) and 4-methylsulfonyl benzaldehyde (647 mg, 3.51 mmol) in CH_2Cl_2 (8 mL) and HOAc (4 mL). The mixture was stirred at rt for 30 min and additional amounts of 1M BH_3•SMe_2 (2 mL, 2 mmol) and 4-methylsulfonyl benzaldehyde (160 mg, 3.51 mmol) were added. After stirring overnight at rt, the solution was concentrated in vacuo, dissolved in CH_2Cl_2 and washed with $NaHCO_3$ solution. The organic layer was dried, concentrated and chromatographed on silica gel eluting with 0-5% MeOH/CH_2Cl_2. This afforded the product as an amber foam: ^{1}H NMR ($CDCl_3$) δ 8.31 (1H, br m), 7.97 (1H, s), 7.86 (2H, d, J = 8 Hz), 7.42 (2H, d, J = 8 Hz), 7.22 (3H, m), 7.02 (2H, dd, J = 8, 2 Hz), 6.58 (1H, s), 4.46 (2H, br), 4.46 (2H, q, J = 7 Hz), 3.87 (2H, s), 3.04 (3H, s), 1.45 (3H, t, J = 7 Hz); HRMS calcd for $C_{23}H_{24}N_2O_4S$+H^+: 425.1535. Found: 425.1524.

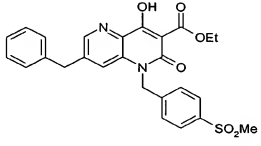
Step 2: Synthesis of ethyl 5-benzyl-3-{(3-ethoxy-3-oxopropanoyl)[4-(methylsulfonyl)benzyl]amino}pyridine-2-carboxylate



A solution of ethyl 5-benzyl-3-{[4-(methylsulfonyl)benzyl]amino}pyridine-2-carboxylate (0.54 g, 1.27 mmol) and ethyl 3-chloro-3-oxopropionate (0.21 mL, 1.67 mmol) in DCE (6 mL) was heated at reflux for 2.5 h. After cooling to rt, the solution

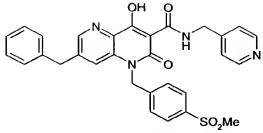
was diluted with CH_2Cl_2 and washed with $NaHCO_3$ solution. The organic layer was dried and concentrated to give the product: ^1H NMR ($CDCl_3$) δ 8.62 (1H, d, J = 2 Hz), 7.82 (2H, d, J = 8 Hz), 7.37 (2H, d, J = 8 Hz), 7.28 (3H, m), 7.06 (1H, d, J = 2 Hz), 6.97 (2H, dd, J = 8, 2 Hz), 5.52 (1H, d, J = 15 Hz), 4.38 (2H, m), 4.22 (1H, d, J = 15 Hz), 4.01 (2H, m), 3.92 (2H, m), 3.24 (1H, d, J = 16 Hz), 3.11 (1H, d, J = 16 Hz), 3.02 (3H, s), 1.39 (3H, t, J = 7 Hz), 1.17 (3H, t, J = 7 Hz); HRMS calcd for $C_{28}H_{30}N_2O_7S+H^+$: 539.1852. Found: 539.1854.

Step 3: Synthesis of ethyl 7-benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate



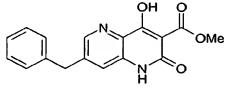
A solution of 1M NaOEt in EtOH (2.5 mL, 2.5 mmol) was added dropwise to a solution of ethyl 5-benzyl-3-{(3-ethoxy-3-oxopropanoyl)[4-(methylsulfonyl)benzyl]-amino}-pyridine-2-carboxylate (690 mg, 1.26 mmol) in EtOH (6 mL). The mixture was stirred at rt for 30 min, neutralized with 1M HCl (2.5 mL) and the resulting precipitate was collected by filtration washing with 1:1 water/EtOH. This procedure afforded the product as an off-white solid: ^1H NMR ($CDCl_3$) δ 14.07 (1H, br s), 8.56 (1H, s), 7.79 (2H, d, J = 8 Hz), 7.30 (3H, m), 7.19 (2H, d, J = 8 Hz), 7.02 (3H, m), 5.40 (2H, br s), 4.53 (2H, q, J = 7 Hz), 4.04 (2H, s), 3.01 (3H, s), 1.48 (3H, s); HRMS calcd for $C_{26}H_{24}N_2O_6S+H^+$: 493.1433. Found: 493.1422.

Example 5: 7-Benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



A mixture of ethyl 7-benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate (40 mg, 0.080 mmol) and 4-(aminomethyl)pyridine (122 μL, 1.2 mmol) in EtOH (1 mL) was heated at 120°C in a sealed tube in a microwave for 30 min. The reaction mixture was concentrated at reduced pressure, reconstituted in CH_2Cl_2 and washed with a mixture of 1N HCl and brine. Drying and evaporation of the organic phase gave the product as a pale green solid: ^{1}H NMR ($CDCl_3$) δ 10.81 (1H, br t, J = 6 Hz), 8.69 (2H, d, J = 7 Hz), 8.65 (1H, d, J = 1 Hz), 7.83 (2H, d, J = 8 Hz), 7.76 (2H, d, J = 6 Hz), 7.31 (3H, m), 7.19 (2H, d, J = 8 Hz), 7.11 (1H, s), 7.03 (2H, m), 5.43 (2H, br s), 4.86 (2H, d, J = 6 Hz), 4.08 (2H, s), 3.03 (3H, s); HRMS calcd for $C_{30}H_{26}N_4O_5S+H^+$: 555.1702. Found: 555.1699.

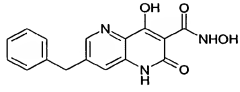
Example 6: Methyl 7-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate



This compound was prepared from ethyl 3-amino-5-benzylpyridine-2-carboxylate and methyl 3-chloro-3-oxopropionate employing methods similar to those described in Example 1, Steps 10-11. The product was obtained as a tan solid: ^{1}H NMR (d_6-DMSO) δ 11.9 (1H, br), 11.59 (1H, s), 8.46 (1H, d, J = 1.6 Hz), 7.43 (1H, d, J = 1.6

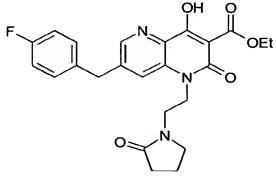
Hz), 7.33-7.20 (5H, m), 4.11 (2H, s), 3.74 (3H, s); HRMS calcd for $C_{17}H_{14}N_2O_4+H^+$: 311.1032. Found: 311.1025.

Example 7 : 7-Benzyl-*N*,4-dihydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



A mixture of methyl 7-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate (21 mg, 68 μmol), hydroxylamine hydrochloride (75 mg, 1.1 mmol) and 4.63 M NaOMe/MeOH (0.1 mL, 463 μmol) in 4:1 EtOH/water (1.25 mL) was heated at reflux for 2 h. The mixture was neutralized with conc. HCl, diluted with water and the resulting solids were collected by filtration. Trituration of the filter cake with EtOAc/MeOH provided the product as a beige solid: ^{1}H NMR (d_6-DMSO) δ 11.86 (2H, br), 9.78 (1H, br), 8.50 (1H, br), 7.50-7.10 (6H, m), 4.10 (2H, br s); HRMS calcd for $C_{16}H_{13}N_3O_4+H^+$: 312.0984. Found: 312.0987.

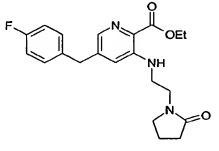
Example 8: Ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate



Step 1: Synthesis of (2-oxopyrrolidin-1-yl)acetaldehyde

Oxalyl chloride (0.87 mL, 10 mmol) was added dropwise to a solution of DMSO (0.71 mL, 10 mmol) in CH_2Cl_2 (7 mL) cooled to –78°C. After stirring 15 min at this temperature, 1-(2-hydroxyethyl)-2-pyrrolidinone (1g, 7.7 mmol) was added dropwise. The mixture was stirred 30 min at –78°C and Et_3N (2.8 mL, 20 mmol) was added dropwise. After allowing the reaction to warm to rt, a solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (6X). The combined organic layers were dried and concentrated to give the product as an oil: ^1H NMR ($CDCl_3$) δ 9.60 (1H, s), 4.16 (2H, s), 3.46 (2H, t, J = 7 Hz), 2.45 (2H, t, J = 8 Hz), 2.11 (2H, m).

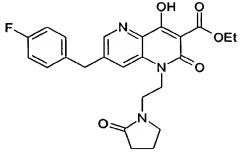
Step 2: Synthesis of ethyl 5-(4-fluorobenzyl)-3-{[2-(2-oxopyrrolidin-1-yl)ethyl]amino}pyridine-2-carboxylate



(2-Oxopyrrolidin-1-yl)acetaldehyde and ethyl 3-amino-5-(4-fluorobenzyl)-2-pyridinecarboxylate were treated in a manner similar to that described in Example 5, Step 1 to yield the product as an amber oil: ^1H NMR ($CDCl_3$) δ 7.89 (1H, d, J = 1.4 Hz), 7.83 (1H, br t, J ~ 6 Hz), 7.15 (2H, dd, J ~ 9, 6 Hz), 6.98 (2H, t, J ~ 9 Hz), 6.92

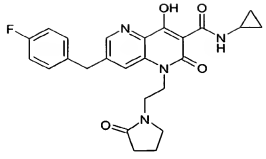
(1H, s), 4.42 (2H, q, J = 7 Hz), 3.92 (2H, s), 3.49 (2H, m), 3.41 (2H, t, J = 7 Hz), 3.35 (2H, q, J = 6 Hz), 2.36 (2H, t, J = 8 Hz), 1.99 (2H, m), 1.42 (3H, t, J = 7 Hz); HRMS calcd for $C_{21}H_{24}FN_3O_3+H^+$: 386.1880. Found: 386.1880.

Steps 3-4: Synthesis of ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate



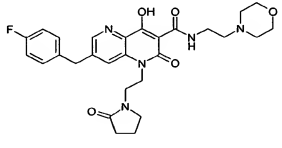
This compound was prepared from ethyl 5-(4-fluorobenzyl)-3-{[2-(2-oxopyrrolidin-1-yl)ethyl]amino}pyridine-2-carboxylate and ethyl 3-chloro-3-oxopropionate in a manner similar to that described in Example 1, Steps 10-11 and was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, d, J = 1.4 Hz), 8.11 (1H, s), 7.26 (2H, m), 7.00 (2H, ddd, J ~ 9, 9, 2 Hz), 4.52 (2H, q, J = 7 Hz), 4.33 (2H, br t, J ~ 7 Hz), 4.14 (2H, s), 3.52-3.44 (4H, m), 2.35 (2H, t, J = 8 Hz), 2.00 (2H, m), 1.48 (3H, t, J = 7 Hz); HRMS calcd for $C_{24}H_{24}FN_3O_5+H^+$: 454.1778. Found: 454.1787.

Example 9: *N*-Cyclopropyl-7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide



A mixture of ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate (47 mg, 104 μmol) and cyclopropylamine (0.1 mL, 1.44 mmol) in EtOH (3 mL) was heated at 120°C in a microwave for 20 min. The mixture was concentrated in vacuo, triturated with EtOH and the product was collected by filtration as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.06 (1H, d, J = 3 Hz), 8.57 (1H, d, J = 1.2 Hz), 8.08 (1H, s), 7.25 (2H, dd, J = 8.5, 5.5 Hz), 7.00 (2H, t, J = 8.5 Hz), 4.32 (2H, q, J = 7 Hz), 4.14 (2H, s), 3.49 (2H, t, J = 7.4 Hz), 3.41 (2H, t, J = 7 Hz), 2.95 (1H, m), 2.32 (2H, t, J = 8 Hz), 1.97 (2H, m), 0.90 (2H, m), 0.69 (2H, m); HRMS calcd for $C_{25}H_{25}FN_4O_4+H^+$: 465.1938. Found: 465.1932.

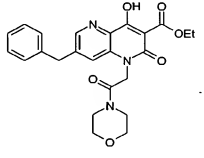
Example 10: 7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-morpholin-4-ylethyl)-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide



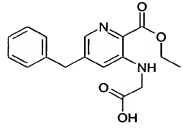
This compound was prepared from ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-(4-

morpholino)ethylamine employing methods similar to those described in Example 6. The reaction mixture was concentrated in vacuo and purified by reverse phase preparative HPLC (C-18 stationary phase; 10-100% CH_3CN/water/0.1% formic acid mobile phase). This procedure gave the product as an off-white rigid foam: ^1H NMR ($CDCl_3$) δ 10.46 (1H, br t, J ~ 6 Hz), 8.59 (1H, d, J = 1.3 Hz), 8.12 (1H, s), 7.24 (2H, dd, J = 8.6, 5.4 Hz), 7.00 (2H, t, J = 8.6 Hz), 4.32 (2H, br t, J = 7 Hz), 4.16 (2H, s), 3.98 (4H, br), 3.91 (2H, q, J = 6 Hz), 3.77 (2H, br), 3.50 (4H, m), 3.39 (2H, t, J = 6 Hz), 2.92 (2H, br), 2.41 (2H, t, J = 8 Hz), 2.05 (2H, m); ES^+ MS: 538 ($M+H^+$, 100).

Example 11: Ethyl 7-benzyl-4-hydroxy-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate

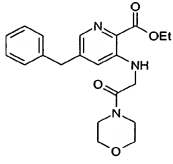


Step 1: Synthesis of *N*-[5-benzyl-2-(ethoxycarbonyl)pyridin-3-yl]glycine



A mixture of ethyl 3-amino-5-benzylpyridine-2-carboxylate (0.543 g, 2.12 mmol) and glyoxylic acid monohydrate (0.254 g, 2.76 mmol) in EtOH (6 mL) was heated at reflux for 1 h. The mixture was allowed to cool to rt and $NaCNBH_3$ (266 mg, 4.23 mmol) was added. After stirring 2 h at rt, the reaction was quenched with water and the EtOH was removed at reduced pressure. The aqueous mixture was extracted with CH_2Cl_2 and the organic layers were dried and concentrated. Trituration of the remaining material with EtOAc/hexanes and filtration afforded the product as a beige solid: : ^1H NMR (d_6-DMSO) δ 13.2 (1H, br), 7.92 (1H, br t, J = 4.8 Hz), 7.76 (1H, s), 7.26 (4H, m), 7.17 (1H, t, J = 7 Hz), 7.00 (1H, s), 4.24 (2H, q, J = 7 Hz), 3.90 (2H, s), 3.86 (2H, br), 1.27 (3H, t, J = 7 Hz).

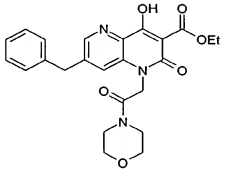
Step 2: Synthesis of 5-benzyl-2-(ethoxycarbonyl)-*N*-(2-morpholin-4-yl-2-oxoethyl)pyridin-3-amine



HATU (494 mg, 1.3 mmol) was added via spatula to a solution of N-[5-benzyl-2-(ethoxycarbonyl)pyridin-3-yl]glycine (328 mg, 1.04 mmol), morpholine (0.113 mL, 1.3 mmol) and Et_3N (0.18 mL, 1.3 mmol) in DMF (6 mL). After stirring for 45 min at rt, the solvent was removed in vacuo and the resulting material was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried and concentrated. Purification of the crude material by silica gel chromatography eluting with 0-5% $MeOH/CH_2Cl_2$ afforded the product: ^1H NMR ($CDCl_3$) δ 8.57 (1H, br), 7.94 (1H, s),

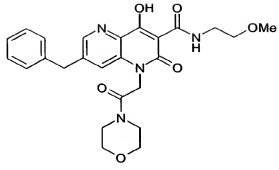
7.23 (3H, m), 7.15 (2H, m), 6.68 (1H, s), 4.46 (2H, q, J = 7 Hz), 3.95 (2H, s), 3.90 (2H, d, J = 4.2 Hz), 3.68 (6H, br), 3.43 (2H, br)1.42 (3H, t, J = 7 Hz); ES^+ MS: 384 ($M+H^+$, 70).

Steps 3-4: Synthesis of ethyl 7-benzyl-4-hydroxy-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate



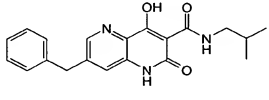
This compound was prepared in two steps from 5-benzyl-2-(ethoxycarbonyl)-*N*-(2-morpholin-4-yl-2-oxoethyl)pyridin-3-amine and ethyl 3-chloro-3-oxopropionate employing methods similar to those described in Example 5, Steps 2-3. The product was obtained as a white solid: ^1H NMR ($CDCl_3$) δ 14.2 (1H, br), 8.53 (1H, s), 7.32 (3H, m), 7.18 (2H, d, J = 7 Hz), 7.05 (1H, s), 4.93 (2H, s), 4.49 (2H, q, J = 7 Hz), 4.13 (2H, s), 3.70 (2H, m), 3.66 (2H, m), 3.54 (4H, m), 1.45 (3H, t, J = 7Hz); ES^+ MS: 452 ($M+H^+$, 100).

Example 12: 7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-benzyl-4-hydroxy-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-methoxyethylamine employing methods similar to those described in Example 6. The product was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.14 (1H, br), 8.59 (1H, s), 7.37-7.27 (3H, m), 7.18 (2H, d, J = 7 Hz), 7.01 (1H, s), 4.93 (2H, s), 4.15 (2H, s), 3.70-3.61 (6H, m), 3.56 (4H, m), 3.52 (2H, m), 3.39 (3H, s); ES$^+$ MS: 481 (M+H$^+$, 100).

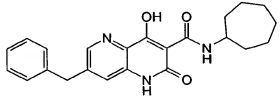
Example 13: 4-Hydroxy-*N*-(2-methylpropyl)-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and isobutylamine employing methods similar to those described in Example 2 and was obtained as a white solid; ^{1}H NMR (d_6-DMSO) δ 10.82 (1H, br), 8.22 (1H, s), 7.35-7.22 (6H, m), 4.03 (2H, s), 3.11 (2H,

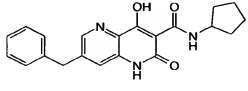
br), 1.77 (1H, m), 0.92 (6H, d, J = 6.5 Hz); HRMS calcd for $C_{20}H_{21}N_3O_3+H^+$: 352.1661. Found: 352.1645.

Example 14: *N*-Cycloheptyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cycloheptylamine employing methods similar to those described in Example 2 and was obtained as a white solid; ^{1}H NMR (d_6-DMSO) δ 10.75 (1H, br), 8.23 (1H, s), 7.38 (1H, s), 7.35-7.20 (5H, m), 4.04 (2H, s), 4.00 (1H, m), 1.88-1.34 (12 H, m); HRMS calcd for $C_{23}H_{25}N_3O_3+H^+$: 392.1974 . Found: 392.1956.

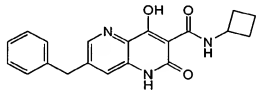
Example 15: *N*-Cyclopentyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclopentylamine employing methods

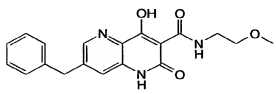
similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 10.75 (1H, br), 8.24 (1H, s), 7.35 (1H, s), 7.32-7.20 (5H, m), 4.21 (1H, m, J = 6.7 Hz), 4.04 (2H, s), 1.93-1.35 (8H, m); Anal. Calcd for $C_{21}H_{21}N_3O_3$.1.90 HCl: C, 58.29; H, 5.33; N, 9.71. Found: C, 58.31;H, 5.33; N, 9.85.

Example 16: *N*-Cyclobutyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



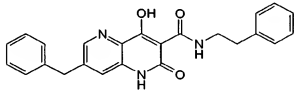
This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclobutylamine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 12.00 (1H, br), 8.23 (1H, br), 7.38-7.25 (6H, m), 4.41 (1H, m, J = 7.7 Hz), 4.04 (2H, br s), 2.27 (2H, br m), 1.93 (2H, br m), 1.71 (2H, br m); Anal. Calcd for $C_{20}H_{19}N_3O_3$. 0.45 CH_2Cl_2: C, 63.37; H, 5.18; N, 10.84. Found: C, 63.62; H, 5.29; N, 10.97.

Example 17: 4-Hydroxy-*N*-[2-(methyloxy)ethyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



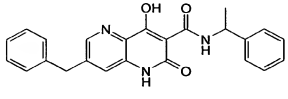
This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-methoxyethylamine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 11.85 (1H, br), 10.80 (1H, br), 9.23 (1H, br), 7.35-7.22 (6H, m), 4.03 (2H, br s), 3.45 (4H, br m), 3.28 (3H, s); Anal. Calcd for $C_{19}H_{19}N_3O_4$. 0.25 CH_2Cl_2: C, 61.72; H, 5.25; N, 11.22. Found: C, 61.44; H, 4.90; N, 11.28.

Example 18: 4-Hydroxy-2-oxo-*N*-(2-phenylethyl)-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



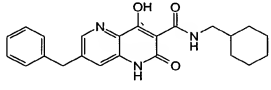
This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and phenethylamine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 11.90 (1H, br), 10.65 (1H br), 8.30 (1H, br), 7.37-7.22 (11H, m), 4.04 (2H, br s), 3.53 (2H, m, J ~ 5 Hz), 2.83 (2H, t, J = 7 Hz); Anal. Calcd for $C_{24}H_{21}N_3O_3$. 0.25 CH_2Cl_2: C, 69.45; H, 5.12; N, 9.92. Found: C, 69.40; H, 4.92; N, 10.11.

Example 19: 4-Hydroxy-2-oxo-*N*-(1-phenylethyl)-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



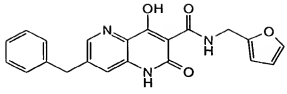
This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2 dihydro-1,5-naphthyridine-3-carboxylate and α-methylbenzylamine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 12.40 (1H, br), 10.80 (1H, br), 8.35 (1H, br), 7.35-7.24 (11H, m), 5.14 (1H, m), 4.05 (2H, br s), 1.46 (3H, br); HRMS calcd for $C_{24}H_{21}N_3O_3+H^+$: 400.1661 . Found: 400.1670.

Example 20: *N*-(Cyclohexylmethyl)-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



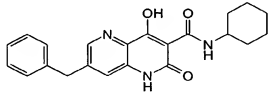
This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2 dihydro-1,5-naphthyridine-3-carboxylate and cyclohexylmethylamine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 10.80 (1H, br), 8.32 (1H, br s), 7.39 (1H, s), 7.35-7.22 (5H, m), 4.05 (2H, br s), 3.17 (2H, t, J = 6 Hz), 1.71-0.79 (11H, m); HRMS calcd for $C_{23}H_{25}N_3O_3+H^+$: 392.1974. Found: 392.1956.

Example 21: *N*-(2-Furanylmethyl)-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



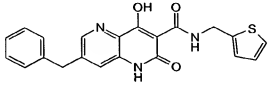
This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and furfurylamine employing methods similar to those described in Example 2 and was obtained as a white solid; ^{1}H NMR (d_6-DMSO) δ 12.13 (1H, br), 11.12 (1H, br), 10.15 (1H, br), 8.20 (1H, br s), 7.57 (1H, s), 7.31-7.20 (6H, m), 6.38 (1H, s), 6.27 (1H, br s), 4.48 (2H, br), 4.01 (2H, br s); HRMS calcd for $C_{21}H_{17}N_3O_4$+H$^+$: 376.1297. Found: 376.1286.

Example 22: *N*-Cyclohexyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



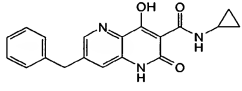
This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclohexylamine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 11.85 (1H, br), 10.60 (1H, br), 8.33 (1H, br), 7.39 (1H, s), 7.35-7.22 (5 H, m), 4.05 (2H, br s), 3.82 (1H, m), 1.85 (2H, m), 1.67 (2H, m), 1.56 (1H, m), 1.38-1.27 (5H, m); HRMS calcd for $C_{22}H_{23}N_3O_3$+H$^+$: 378.1810. Found: 378.1822.

Example 23: 4-Hydroxy-2-oxo-7-(phenylmethyl)-*N*-(2-thienylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and thiophene-2-methylamine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 12.25 (1H, br), 11.10 (1H, br), 10.2 (1H, br), 8.28 (1H, br s), 7.38 (1H, br s), 7.34-7.22 (6H, m), 7.04 (1H, s), 6.97 (1H, d, J = 4.3 Hz), 4.68 (2H, br), 4.04 (2H, br s); HRMS calcd for $C_{21}H_{17}N_3O_3S+H^+$: 392.1069. Found: 392.1070.

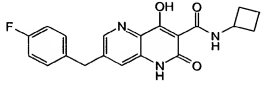
Example 24: *N*-Cyclopropyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclopropylamine employing methods similar to those described in Example 11 and using dimethylacetamide as the reaction solvent. The product was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 11.86 (1H, s), 10.87 (1H, s), 10.14 (1H, s), 8.20 (1H, s), 7.38-7.25 (6H, m), 4.01 (2H, br s),

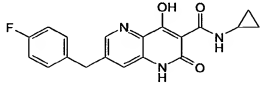
2.79 (1H, m), 0.70 (2H, m), 0.45 (2H, m); HRMS calcd for $C_{19}H_{17}N_3O_3+H^+$: 336.1348. Found: 336.1347.

Example 25: *N*-Cyclobutyl-7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclobutylamine employing methods similar to those described in Example 2 and was obtained as an off-white solid: ^{1}H NMR (d_6-DMSO) δ 11.90 (1H, br), 10.50 (1H, br), 8.33 (1H, br), 7.39 (1H, br s), 7.31 (2H, m), 7.15 (2H, t, J ~ 9Hz), 4.42 (1H, m, J = 8 Hz), 4.06 (2H, br s), 2.29 (2H, m), 1.95 (2H, m), 1.71 (2H, m); HRMS calcd for $C_{20}H_{18}FN_3O_3+H^+$: 368.1410. Found: 368.1410.

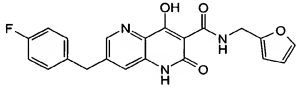
Example 26: *N*-Cyclopropyl-7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclopropylamine employing

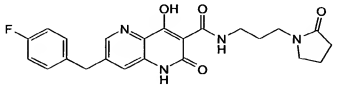
methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 11.80 (1H, br), 10.35 (1H, br), 8.35 (1H, br), 7.38 (1H, s), 7.30 (2H, m), 7.15 (2H, t, J = 8.7 Hz), 4.06 (2H, br s), 2.85 (1H, m), 0.74 (2H, m), 0.51 (2H, m); HRMS calcd for $C_{19}H_{16}FN_3O_3+H^+$: 354.1254. Found: 354.1255.

Example 27: 7-[(4-Fluorophenyl)methyl]-*N*-(2-furanylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



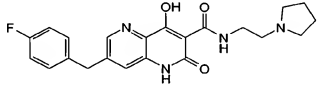
This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and furfurylamine employing methods similar to those described in Example 2 and was obtained as an off-white solid: ^{1}H NMR (d_6-DMSO) δ 11.85 (1H, br), 10.70 (1H, br), 8.39 (1H, br s), 7.61 (1H, s), 7.40 (1H, s), 7.31 (2H, m), 7.15 (2H, t, J = 8.5 Hz), 6.42 (1H, s), 6.33 (1H, s), 4.54 (2H, s), 4.08 (2H, s); HRMS calcd for $C_{21}H_{16}FN_3O_4+H^+$: 394.1202. Found: 394.1195.

Example 28: 7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[3-(2-oxo-1-pyrrolidinyl)propyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide



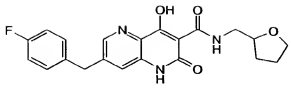
This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 1-(3-aminopropyl)-2-pyrrolidinone employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 1.88 (1H, br), 10.82 (1H, br), 10.12 (1H, br), 8.20 (1H, m), 7.38 (1H, s), 7.29 (2H, m), 7.17 (2H, m), 4.01 (2H, s), 3.27-3.22 (6H, m), 2.21 (2H, t, J = 8 Hz), 1.91 (2H, m), 1.69 (2H, m); HRMS calcd for $C_{23}H_{23}FN_4O_4$+H$^+$: 439.1782. Found: 439.1774.

Example 29 7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[2-(1-pyrrolidinyl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide



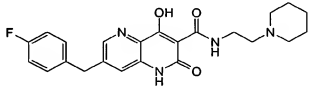
This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-(1-pyrrolidinyl)ethylamine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 10.61 (1H, br), 8.28 (1H, br s), 7.36 (1H, s), 7.30 (2H, m), 7.14 (2H, t, J = 8.8 Hz), 4.04 (2H, s), 3.41 (2H, m), 2.56 (2H, t, J = 6.4 Hz), 2.54-2.48 (4H, m), 1.68 (4H, m); ES$^+$ MS: 411 (M+H$^+$, 100).

Example 30: (±)-7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(tetrahydro-2-furnylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



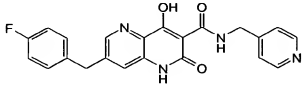
This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and (±)-(tetrahydro-2-furanylmethyl)amine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 11.9 (1H, br), 10.60 (1H, br), 8.37 (1H, br), 7.39 (1H, s), 7.30 (2H, m), 7.15 (2H, t, J = 8.6 Hz), 4.06 (2H, br s), 3.96 (1H, m), 3.80 (1H, q, J ~ 7 Hz), 3.64 (1H, q, J ~ 7 Hz), 3.50-3.20 (2H, m), 2.00-1.52 (4H, m); ES$^+$ MS: 398 (M+H$^+$, 100).

Example 31: 7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[2-(1-piperidinyl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide



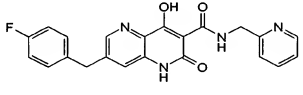
This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-(1-piperidinyl)ethylamine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 11.75 (1H, br), 10.70 (1H, br), 10.15 (1H, br), 8.20 (1H, m), 7.38-7.11 (5H, m), 4.01 (2H, s), 3.39 (2H, m), 2.38 (6H, m), 1.50 (4H, m), 1.39 (2H, m); ES$^+$ MS: 425 (M+H$^+$, 100).

Example 32: 7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(4-pyridinylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



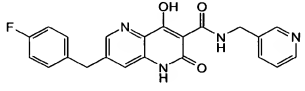
This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 4-(aminomethyl)pyridine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 12.40 (1H, br), 11.31 (1H, br), 10.15 (1H, br), 8.48 (2H, br m), 8.20 (1H, br s), 7.29 (5H, m), 7.14 (2H, t, J = 8.7 Hz), 4.52 (2H, br m), 4.01 (2H, s); ES$^+$ MS: 405 (M+H$^+$, 100).

Example 33: 7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(2-pyridinylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



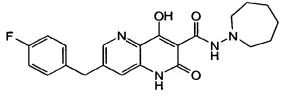
This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-(aminomethyl)pyridine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 12.30 (1H, br), 11.21 (1H, br), 10.20 (1H, br), 8.52 (1H, d, J = 4.2 Hz), 8.26 (1H, br s), 7.75 (1H, t, J = 7.6 Hz), 7.36-7.24 (5H, m), 7.15 (2H, t, J = 8.9 Hz), 4.62 (2H, br m), 4.04 (2H, s); ES$^+$ MS: 405 (M+H , 100).

Example 34: 7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(3-pyridinylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 3-(aminomethyl)pyridine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 12.32 (1H, br), 11.29 (1H, br), 10.17 (1H, br), 8.56 (1H, s), 8.44 (1H, br), 8.18 (1H, br), 7.73 (1H, m), 7.30-7.27 (4H, m), 7.14 (2H, t, J = 8.6 Hz), 4.55 (2H, m), 4.01 (2H, s); ES$^+$ MS: 405 (M+H$^+$, 100).

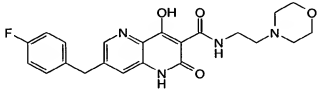
Example 35: 7-[(4-Fluorophenyl)methyl]-*N*-(hexahydro-1*H*-azepin-1-yl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and hexahydro-1-*H*-azepin-1-amine employing methods similar to those described in Example 2 and was obtained as a white solid: : ^{1}H NMR (d_6-DMSO) δ 12.90 (1H, br), 11.80 (1H, br), 10.13 (1H, br),

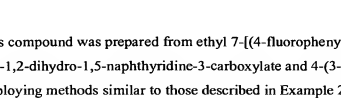
8.15 (1H, br s), 7.23 (3H, m), 7.11 (2H, t, J = 8.8 Hz), 3.97 (2H, s), 2.94 (4H, m), 1.59 (8H, m); ES^+ MS: 411 ($M+H^+$, 100).

Example 36: 7-[(4-Fluorophenyl)methyl]-4-hydroxy-*N*-[2-(4-morpholinyl)ethyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-(4-morpholino)ethylamine employing methods similar to those described in Example 2 and was obtained as a white solid: : ^1H NMR (d_6-DMSO) δ 11.79 (1H, s), 10.76 (1H, br s), 10.12 (1H, br), 8.18 (1H, m), 7.35-7.24 (3H, m), 7.12 (2H, br m), 3.98 (2H, br s), 3.56 (4H, m), 3.40 (2H, m), 2.39 (6H, m); ES^+ MS: 427 ($M+H^+$, 100).

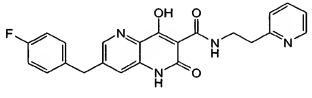
Example 37: 7-[(5-Fluoro-2-pyridinyl)methyl]-4-hydroxy-*N*-[3-(4-morpholinyl)propyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 4-(3-aminopropyl)morpholine employing methods similar to those described in Example 2 and was obtained as a

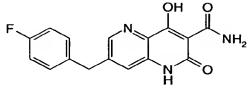
white solid: : ^{1}H NMR (CF_3CO_2D) δ 8.71 (1H, s), 8.47 (1H, s), 7.28 (2H, dd, J = 8.5, 5.3 Hz), 7.13 (2H, t, J = 8.5 Hz), 4.41 (2H, s), 4.38 (2H, m), 4.13 (2H, m), 3.82 (4H, m), 3.54 (2H, t, J = 8 Hz), 3.43 (2H, m), 2.41 (2H, m); ES^+ MS: 441 (M+H , 100).

Example 38: 7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[2-(2-pyridinyl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide



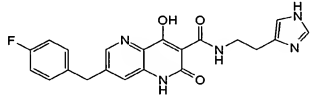
This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-(2-aminoethyl)pyridine employing methods similar to those described in Example 2 and was obtained as a white solid: ^{1}H NMR (CF_3CO_2D) δ 8.84 (1H, d, J = 6 Hz), 8.79 (1H, s), 8.71 (1H, t, J = 8 Hz), 8.55 (1H s), 8.20 (1H, d, J = 8 Hz), 8.11 (1H, t, J = 7 Hz), 7.35 (2H, dd, J = 8.6, 5.3 Hz), 7.20 (2H, t, J = 8.6 Hz), 4.48 (2H, s), 4.26 (2H, t, J = 7 Hz), 3.75 (2H, t, J = 7 Hz); ES^+ MS: 4419 ($M+H^+$, 100).

Example 39: 7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



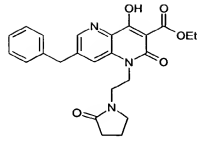
This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and ammonium hydroxide employing methods similar to those described in Example 11 and was obtained as a light yellow solid: ^{1}H NMR (CF_3CO_2D) δ 8.77 (1H, s), 8.51 (1H, s), 7.29 (2H, dd, J = 8.6, 5.1 Hz), 7.13 (2H, t, J = 8.6 Hz), 4.43 (2H, s); ES^+ MS: 314 ($M+H^+$, 100).

Example 40: 7-[(4-Fluorophenyl)methyl]-4-hydroxy-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



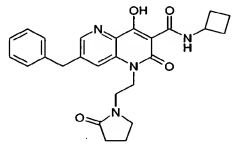
This compound was prepared from ethyl 7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-(1*H*-imidazol-4-yl)ethylamine employing methods similar to those described in Example 11 and was obtained as an off-white solid: ^{1}H NMR (CF_3CO_2D) δ 8.66 (1H, s), 8.60 (1H, s), 8.43 (1H, s), 7.39 (1H, s), 7.22 (2H, m), 7.08 (2H, t, J = 8.4 Hz), 4.36 (2H, s), 4.00 (2H, br, t, J = 6 Hz), 3.29 (2H, br t, J = 6 Hz); ES^+ MS: 408 ($M+H^+$, 100).

Example 41: Ethyl 7-benzyl-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate



This compound was prepared from ethyl 3-amino-5-benzylpyridine-2-carboxylate and (2-oxopyrrolidin-1-yl)acetaldehyde employing methods similar to those described in Example 10, Steps 1-4 and was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 13.9 (1H, br), 8.54 (1H, s), 8.11 (1H, s), 7.52-7.21 (5H, m), 4.52 (2H, q, J = 7 Hz), 4.34 (2H, br t, J = 7 Hz), 4.18 (2H, s), 3.52 (2H, br t, J = 7 Hz), 3.44 (2H, t, J = 7 Hz), 2.33 (2H, t, J = 8 Hz), 1.98 (2H, m), 1.48 (3H, t, J = 7 Hz); ES$^+$ MS: 458 (M+Na$^+$, 100).

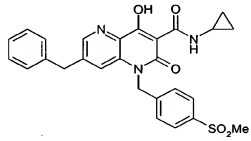
Example 42: Benzyl-*N*-cyclobutyl-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-benzyl-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclobutylamine employing methods similar to those described in Example 2 and was obtained as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 10.23 (1H, br d, J = 7 Hz), 8.58

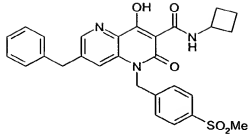
(1H, s), 8.02 (1H, s), 7.33-7.20 (5H, m), 4.53 (1H, m), 4.35 (2H, br t, J = 7 Hz), 4.17 (2H, s), 3.52 (2H, t, J = 7 Hz), 3.37 (2H, t, J = 7 Hz), 2.41 (2H, m), 2.28 (2H, t, J = 8 Hz), 2.08 (2H, m), 1.93 (2H, m), 1.80 (2H, m); HRMS calcd for $C_{26}H_{28}N_4O_4+H^+$: 461.2189. Found: 461.2205.

Example 43: 7-Benzyl-*N*-cyclopropyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



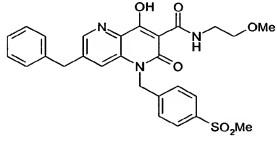
This compound was prepared from ethyl 7-benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclopropylamine employing methods similar to those described in Example 2. The product was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.04 (1H, br d, J = 3.4 Hz), 8.61 (1H, s), 7.81 (2H, d, J = 8.4 Hz), 7.29 (3H, m), 7.17 (2H, d, J = 8.4 Hz), 7.05 (1H, s), 7.03 (2H, m), 5.39 (2H, br), 4.05 (2H, s), 3.01 (3H, s), 2.97 (1H, m), 0.90 (2H, m), 0.70 (2H, m); HRMS calcd for $C_{27}H_{25}N_3O_5S+H^+$: 504.1593. Found: 504.1581.

Example 44: 7-Benzyl-*N*-cyclobutyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclobutylamine employing methods similar to those described in Example 2. The product was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.19 (1H, br d, J = 7.4 Hz), 8.61 (1H, d, J = 1.1 Hz), 7.82 (2H, d, J = 8.4 Hz), 7.30 (3H, m), 7.18 (2H, d, J = 8.4 Hz),7.06 (1H, s), 7.03 (2H, m), 5.41 (2H, br), 4.54 (1H, m), 4.05 (2H, s), 3.02 (3H, s), 2.44 (2H, m), 2.08 (2H, m), 1.83 (2H, m); HRMS calcd for $C_{28}H_{27}N_3O_5S+H^+$: 518.1740. Found: 518.1741.

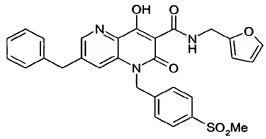
Example 45: 7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-methoxyethylamine employing methods similar to those described in Example 2. The product was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.22 (1H, br m), 8.61

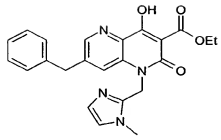
(1H, s), 7.81 (2H, d, J = 8 Hz), 7.29 (3H, m), 7.17 (2H, d, J = 8 Hz), 7.06 (1H, s), 7.02 (2H, m), 5.41 (2H, br), 4.05 (2H, s), 3.67 (2H, m), 3.60 (2H, m), 3.40 (3H, s), 3.01 (3H, s); HRMS calcd for $C_{27}H_{27}N_3O_6S+H^+$: 522.1699. Found: 522.1686.

Example 46: 7-Benzyl-*N*-(2-furylmethyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



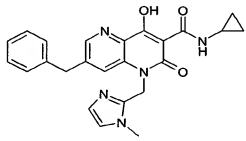
This compound was prepared from ethyl 7-benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and furfurylamine employing methods similar to those described in Example 2. The product was obtained as a light beige solid: ^{1}H NMR ($CDCl_3$) δ 10.37 (1H, br t, J = 5.5 Hz), 8.62 (1H, s), 7.81 (2H, d, J = 8 Hz), 7.39 (1H, s), 7.30 (3H, m), 7.17 (2H, d, J = 8 Hz), 7.06 (1H, s), 7.03 (2H, m), 6.33 (2H, m), 5.40 (2H, br), 4.66 (2H, br d, J = 5.5 Hz), 4.05 (2H, s), 3.01 (3H, s); HRMS calcd for $C_{29}H_{25}N_3O_6S+H^+$: 544.1542. Found: 544.1534.

Example 47: Ethyl 7-benzyl-4-hydroxy-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate



This compound was prepared from ethyl 3-amino-5-benzylpyridine-2-carboxylate and 1-methyl-2-imidazolecarboxaldehyde employing methods similar to those describe in Example 5, Steps 1-3. The product was obtained as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 13.7 (1H, br), 8.50 (2H, s), 7.28-7.21 (5H, m), 6.99 (1H, br s), 6.81 (1H, s), 5.66 (2H, br), 4.52 (2H, q, J = 7 Hz), 4.17 (2H, s), 3.72 (3H, s), 1.46 (3H, t, J = 7 Hz); HRMS calcd for $C_{23}H_{22}N_4O_4+H^+$: 419.1719. Found: 419.1711.

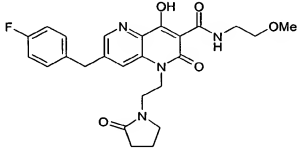
Example 48: 7-Benzyl-*N*-cyclopropyl-4-hydroxy-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-benzyl-4-hydroxy-1-[(1-methyl-1H-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclopropylamine using methods similar to those described in Example 11. The product was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.02 (1H, br), 8.57 (1H,

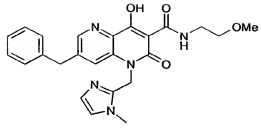
s), 8.45 (1H, br s), 7.30-7.21 (5H, m), 7.01 (1H, br s), 6.83 (1H, s), 5.69 (2H, br), 4.17 (2H, s), 3.67 (3H, s), 2.95 (1H, m), 0.91 (2H, m), 0.71 (2H, m); HRMS calcd for $C_{24}H_{23}N_5O_3+H^+$: 430.1879. Found: 430.1877.

Example 49: 7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide



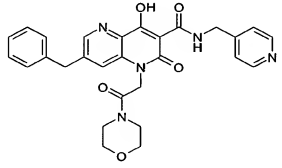
This compound was prepared from ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-methoxyethylamine by methods similar to those described in Example 6. The product was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.27 (1H, br m), 8.55 (1H, s), 8.06 (1H, s), 7.24 (2H, m), 6.99 (2H, t, J = 8.6 Hz), 4.35 (2H, t, J = 7 Hz), 4.14 (2H, s), 3.65 (2H, m), 3.59 (2H, m), 3.50 (2H, t, J = 7 Hz), 3.44 (2H, m), 3.42 (3H, s), 2.31 (2H, t, J = 8 Hz), 1.97 (2H, m); ES$^+$MS: 483 (M+H$^+$, 100).

Example 50: 7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-benzyl-4-hydroxy-1-[(1-methyl-1H-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-methoxyethylamine employing methods similar to those described in Example 6. The product was obtained as a beige powder: ^{1}H NMR ($CDCl_3$) δ 10.14 (1H, br), 8.58 (2H, br), 7.32-7.15 (5H, m), 7.12 (1H, br), 6.88 (1H, br s), 5.97 (2H, br), 4.22 (2H, s), 3.70 (3H, s), 3.67 (2H, q, J ~ 5 Hz), 3.60 (2H, t, J ~ 5 Hz), 3.42 (3H, s); ES$^+$ MS: 483 ($M+H^+$, 100).

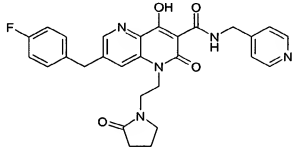
Example 51: 7-Benzyl-4-hydroxy-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-benzyl-4-hydroxy-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 4-(aminomethyl)pyridine employing methods similar to those employed in Example 11.

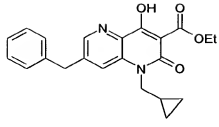
The product was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.48 (1H, br t, J = 6 Hz), 8.62 (1H, d, J = 1.1 Hz), 8.58 (2H, d, J = 6 Hz), 7.38-7.29 (3H, m), 7.27 (2H, d, J = 6 Hz), 7.19 (2H, d, J = 7 Hz), 7.02 (1H, s), 4.93 (2H, s), 4.65 (2H, d, J = 6 Hz), 4.16 (2H, s), 3.69 (4H, m), 3.57 (2H, m), 3.51 (2H, m); ES^+ MS: 514 ($M+H^+$, 100).

Example 52: 7-(4-Fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



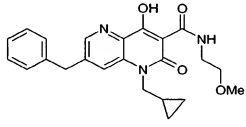
This compound was prepared from ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 4-(aminomethyl)pyridine employing procedures similar to those described in Example 12. The product was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 14.4 (1H, br), 10.84 (1H, br t, J = 6 Hz), 8.83 (2H, d, J = 6.5 Hz), 8.63 (1H, s), 8.10 (1H, s), 7.79 (2H, d, J = 6.5 Hz), 7.24 (2H, m), 7.01 (2H, t, J = 8.6 Hz), 4.86 (2H, d, J = 6 Hz), 4.38 (2H, t, J = 7 Hz), 4.17 (2H, s), 3.54-3.47 (4H, m), 2.40 (2H, t, J = 8 Hz), 2.04 (2H, m); ES^+ MS: 516 ($M+H^+$, 100).

Example 53:. Ethyl 7-benzyl-1-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate



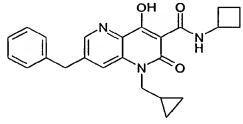
This compound was prepared from ethyl 3-amino-5-benzylpyridine-2-carboxylate and cyclopropanecarboxaldehyde employing methods similar to those described in Example 5, Steps 1-3 and was obtained as a tan wax: ^{1}H NMR (d_6-DMSO) δ 11.65 (1H, br), 8.47 (1H, s), 8.03 (1H, s), 7.34-7.28 (4H, m), 7.20 (1H, t, J = 7 Hz), 4.22 (2H, q, J = 7 Hz), 4.17 (2H, s), 4.07 (2H, d, J = 7 Hz), 1.23 (3H, t, J = 7 Hz), 1.10 (1H, m), 0.38 (4H, m); HRMS calcd for $C_{22}H_{22}N_2O_4$+H$^+$: 379.1658. Found: 379.1673.

Example 54: 7-Benzyl-1-(cyclopropylmethyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



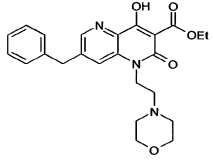
This compound was prepared from ethyl 7-benzyl-1-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-methoxyethylamine employing methods similar to those described in Example 6 and was obtained as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 10.36 (1H, br t, J = 5 Hz), 8.59 (1H, d, J = 1.3 Hz), 7.46 (1H, s), 7.34 (2H, m), 7.26 (1H, m), 7.20 (2H, d, J = 7 Hz), 4.16 (2H, s), 4.08 (2H, d, J = 7 Hz), 3.64 (2H, q, J ~ 5 Hz), 3.58 (2H, t, J ~ 5 Hz), 3.40 (3H, s), 1.00 (1H, m), 0.46 (2H, m), 0.39 (2H, m); HRMS calcd for $C_{23}H_{25}N_3O_4$+H$^+$: 408.1923. Found: 408.1914.

Example 55: 7-Benzyl-*N*-cyclobutyl-1-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



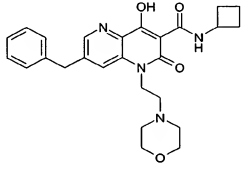
This compound was prepared from ethyl 7-benzyl-1-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclobutylamine employing methods similar to those described in Example 6 and was obtained as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 10.34 (1H, br d, J = 7 Hz), 8.59 (1H, s), 7.46 (1H, s), 7.35 (2H, t, J = 7 Hz), 7.28 (1H, t, J = 7 Hz), 7.21 (2H, d, J = 7 Hz), 4.53 (1H, m), 4.17 (2H, s), 4.08 (2H, d, J = 7 Hz), 2.42 (2H, m), 2.09 (2H, m), 1.80 (2H, m), 1.01 (1H, m), 0.50 (2H, m), 0.40 (2H, m); HRMS calcd for $C_{24}H_{25}N_3O_3$+H$^+$: 404.1974. Found: 404.1971.

Example 56: Ethyl 7-benzyl-4-hydroxy-1-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate



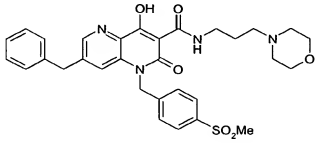
This compound was prepared from ethyl 3-amino-5-benzylpyridine-2-carboxylate and morpholin-4-ylacetaldehyde (Duhamel, L. et al.; Bull. Soc. Chim. Fr.; 1968; 4423-4428) employing methods similar to those described in Example 5, Steps 1-3 and was obtained as an amber glass: ^{1}H NMR ($CDCl_3$) δ 8.54 (1H, d, J = 1 Hz), 8.45 (1H, br), 7.35-7.26 (4H, m), 7.20 (1H, t, J = 7 Hz), 4.72 (2H, br), 4.51 (2H, q, J = 7 Hz), 4.22 (2H, s), 4.02 (6H, br), 3.06 (4H, br), 1.46 (3H, t, J = 7 Hz); HRMS calcd for $C_{24}H_{27}N_3O_5$+H$^+$: 438.2029. Found: 438.2021.

Example 57: 7-Benzyl-*N*-cyclobutyl-4-hydroxy-1-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



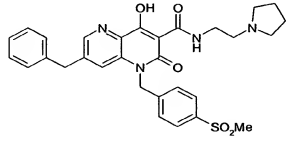
This compound was prepared from ethyl 7-benzyl-4-hydroxy-1-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclobutylamine employing methods similar to those described in Example 6 and was obtained as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 10.01 (1H, br d, J = 5 Hz), 8.70 (1H, s), 8.61 (1H, s), 7.39 (2H, d, J = 7.7 Hz), 7.30 (2H, t, J = 7.7 Hz), 7.21 (1H, m), 4.89 (2H, m), 4.52 (1H, m), 4.26 (4H, m), 4.07 (2H, m), 3.50 (2H, m), 3.18 (2H, m), 3.09 (2H, m), 2.43 (2H, m), 2.06 (2H, m), 1.81 (2H, m); HRMS calcd for $C_{26}H_{30}N_4O_4$+H$^+$: 463.2345. Found: 463.2343.

Example 58: 7-Benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-*N*-(3-morpholin-4-ylpropyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



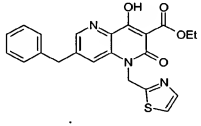
This compound was prepared from ethyl 7-benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and N-(3-aminopropyl)morpholine employing methods similar to those described in Example 6 and was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 13.29 (1H, br), 10.31 (1H, t, J = 6 Hz), 8.62 (1H, d, J = 1 Hz), 7.82 (2H, d, J = 8.3 Hz), 7.30 (3H, m), 7.18 (2H, d, J = 8.3 Hz), 7.07 (1H, s), 7.03 (2H, m), 5.40 (2H, br), 4.32 (2H, m), 4.06 (2H, s), 3.97 (2H, m), 3.60 (2H, m), 3.46 (2H, m), 3.08 (2H, m), 3.02 (3H, s), 2.87 (2H, m), 2.34 (2H, m); HRMS calcd for $C_{31}H_{34}N_4O_6S+H^+$: 591.2277. Found: 591.2277.

Example 59: 7-Benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(2-pyrrolidin-1-ylethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



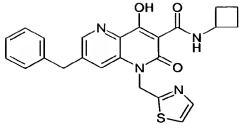
This compound was prepared from ethyl 7-benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and N-(2-aminoethyl)pyrrolidine employing methods similar to those described in Example 6 and was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 12.80 (1H, br), 10.44 (1H, t, J = 6 Hz), 8.60 (1H, d, J = 1 Hz), 7.81 (2H, d, J = 8.2 Hz), 7.30 (3H, m), 7.19 (2H, d, J = 8.2 Hz), 7.06 (1H, s), 7.01 (2H, m), 5.41 (2H, br), 4.05 (2H, s), 4.02 (2H, q, J = 6.6 Hz), 3.87 (2H, br), 3.36 (2H, t, J = 7 Hz), 3.02 (3H, s), 2.89 (2H, m), 2.24 (2H, br), 2.10 (2H, br); HRMS calcd for $C_{30}H_{32}N_4O_5S+H^+$: 561.2172. Found: 561.2166.

Example 60: Ethyl 7-benzyl-4-hydroxy-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate



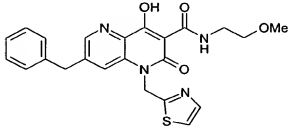
This compound was prepared from ethyl 3-amino-5-benzylpyridine-2-carboxylate and 2-thiazolecarboxaldehyde employing methods similar to those described in Example 5, Steps 1-3 and was obtained as a white solid; ^{1}H NMR (d_6-DMSO) δ 8.49 (1H, s), 8.05 (1H, s), 7.68 (1H, d, J = 3.3 Hz), 7.65 (1H, d, J = 3.3 Hz), 7.28-7.15 (5H, m), 5.69 (2H, s), 4.23 (2H, q, J = 7 Hz), 4.09 (2H, s), 1.24 (3H, t, J = 7 Hz); HRMS calcd for $C_{22}H_{19}N_3O_4S+H^+$: 422.1175. Found: 422.1164.

Example 61: 7-Benzyl-*N*-cyclobutyl-4-hydroxy-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-benzyl-4-hydroxy-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclobutylamine employing methods similar to those described in Example 6 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 10.27 (1H, d, J = 7), 8.56 (1H, s), 8.13 (1H, s), 7.70 (1H, d, J = 3.2 Hz), 7.67 (1H, d, J = 3.2 Hz), 7.28-7.16 (5H, m), 5.78 (2H, s), 4.41 (1H, m), 4.09 (2H, s), 2.29 (2H, m), 2.05 (2H, m), 1.71 (2H, m); HRMS calcd for $C_{24}H_{22}N_4O_3S+H^+$: 447.1491. Found: 447.1487.

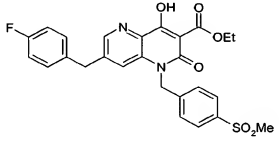
Example 62: 7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-benzyl-4-hydroxy-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-methoxyethylamine employing methods similar to those described in Example 6 and was obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 10.21 (1H, t, J = 5 Hz), 8.56 (1H, s), 8.12 (1H, s), 7.69 (1H, d, J = 3.2 Hz), 7.67 (1H, d, J = 3.2 Hz) 7.28-7.22 (4H, m), 7.18 (1H, t, J = 7

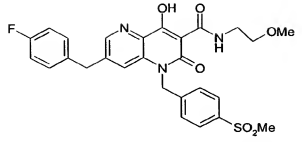
Hz), 5.78 (2H, s), 4.09 (2H, s), 3.56-3.48 (4H, m), 3.28 (3H, s); HRMS calcd for $C_{23}H_{22}N_4O_4S+H^+$: 451.1440. Found: 451.1428.

Example 63:. Ethyl 7-(4-fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate



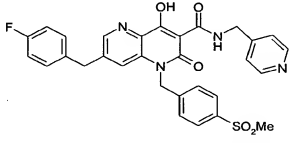
This compound was prepared from ethyl 3-amino-5-(4-fluorobenzyl)-2-pyridinecarboxylate and 4-methylsulfonyl benzaldehyde employing methods similar to those described in Example 5, Steps 1-3 and was obtained as a white solid; ^1H NMR (d_6-DMSO) δ 8.49 (1H, s), 7.83 (2H, d, J = 8.3 Hz), 7.73 (1H, s), 7.38 (2H, d, J = 8.3 Hz), 7.18 (2H, dd, J = 8.2, 6 Hz), 7.04 (2H, t, J = 9 Hz), 5.51 (2H, s), 4.25 (2H, q, J = 7 Hz), 4.04 (2H, s), 3.15 (3H, s), 1.25 (3H, t, J = 7 Hz); ES^+ MS: 511 ($M+H^+$, 100).

Example 64: 7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-(4-fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-methoxyethylamine employing methods similar to those described in Example 6 and was obtained as a white solid; ^{1}H NMR ($CDCl_3$) δ 10.22 (1H, br t, J = 5 Hz), 8.58 (1H, d, J = 1.2 Hz), 7.85 (2H, d, J = 8.3 Hz), 7.21 (2H, d, J = 8.3 Hz), 7.01-6.98 (5H, m), 5.44 (2H, br), 4.02 (2H, s), 3.68 (2H, q, J = 5.2 Hz), 3.60 (2H, t, J = 5.2 Hz); 3.41 (3H, s), 3.03 (3H, s); ES^+ MS: 540 ($M+H^+$, 100).

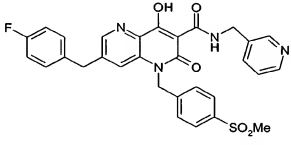
Example 65: 7-(4-Fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-(4-fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 4-(aminomethyl)pyridine employing methods similar to those described in Example 6 and was obtained as a white solid; ^{1}H NMR ($CDCl_3$) δ 10.59 (1H, t, J ~ 6 Hz), 8.64 (2H, d, J = 6 Hz), 8.62 (1H, d, J = 1.2 Hz), 7.86 (2H, d, J = 8 Hz), 7.55 (2H,

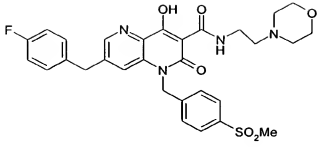
d, J = 6 Hz), 7.22 (2H, d, J = 8 Hz), 7.06 (1H, s), 7.00 (4H, m), 5.43 (2H, br), 4.78 (2H, d, J = 6 Hz), 4.05 (2H, s), 3.04 (3H, s); ES^+ MS: 573 ($M+H^+$, 100).

Example 66. 7-(4-Fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(pyridin-3-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



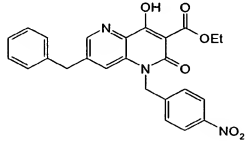
This compound was prepared from ethyl 7-(4-fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 3-(aminomethyl)pyridine employing methods similar to those described in Example 6 and was obtained as a white solid; ^1H NMR ($CDCl_3$) δ 10.82 (1H, br t, J = 6 Hz), 8.79 (1H, s), 8.67 (1H, d, J = 5 Hz), 8.61 (1H, s), 8.44 (1H, d, J = 8 Hz), 7.90 (1H, m), 7.86 (2H, d, J = 8.2 Hz), 7.22 (2H, d, J = 8.2 Hz), 7.07 (1H, s), 7.00 (4H, m), 5.44 (2H, br), 4.83 (2H, d, J = 6 Hz), 4.05 (2H, s), 3.04 (3H, s); ES^+ MS: 573 ($M+H^+$, 100).

Example 67: 7-(4-Fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-*N*-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-(4-fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-(4-morpholino)ethylamine employing methods similar to those described in Example 6 and was obtained as a white solid; ^{1}H NMR ($CDCl_3$) δ 13.49 (1H, br), 10.45 (1H, t, J = 6 Hz), 8.57 (1H, s), 7.84 (2H, d, J = 8.3 Hz), 7.23 (2H, d, J = 8.3 Hz), 7.04 (1H, s), 7.00 (4H, m), 5.43 (2H, br), 4.31 (2H, m), 4.08 (2H, m), 4.02 (2H, s), 3.99 (2H, m), 3.58 (2H, m), 3.29 (2H, m), 3.03 (3H, s), 2.97 (2H, m); ES$^+$ MS: 595 ($M+H^+$, 100).

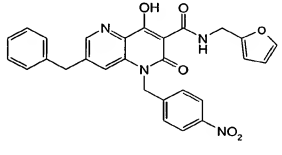
Example 68: Ethyl 4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate



This compound was prepared from ethyl 3-amino-5-benzylpyridine-2-carboxylate and 4-nitrobenzaldehyde employing methods similar to those described in Example 5,

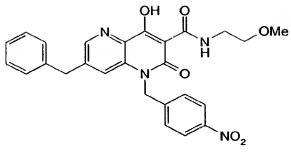
Steps 1-3 and was obtained as a beige solid: ^{1}H NMR (d_6-DMSO) δ 8.14 (2H, d, J = 8.6 Hz), 8.10 (1H, s), 7.36 (2H, d, J = 8.6 Hz), 7.29 (1H, s), 7.14 (3H, m), 7.07 (2H, m), 5.43 (2H, br), 4.08 (2H, q, J = 7 Hz), 3.92 (2H, s), 1.21 (3H, t, J = 7 Hz); ES$^+$ MS: 460 (M+H$^+$, 30).

Example 69: *N*-(2-Furanylmethyl)-4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



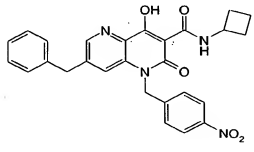
This compound was prepared from ethyl 4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and furfurylamine employing methods similar to those described in Example 2 and was obtained as a beige solid: ^{1}H NMR (d_6-DMSO) δ 11.10 (1H, br m), 8.21 (1H, s), 8.10 (2H, d, J = 8.6 Hz), 7.57 (1H, s), 7.35 (2H, d, J = 8.6 Hz), 7.30 (1H, s), 7.13 (3H, m), 7.06 (2H, m), 6.39 (1H, br s), 6.27 (1H, d, J = 3 Hz), 5.48 (2H, br), 4.45 (2H, d, J = 5 Hz), 3.91 (2H, s); HRMS calcd for $C_{28}H_{22}N_4O_6$+H$^+$: 511.1618. Found: 511.1609.

Example 70: 4-Hydroxy-*N*-[2-(methyloxy)ethyl]-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-methoxyethylamine employing methods similar to those described in Example 2 and was obtained as a light yellow solid: ^{1}H NMR (d_6-DMSO) δ 10.69 (1H, br), 8.21 (1H, s), 8.10 (2H, d, J = 8.7 Hz), 7.35 (2H, d, J = 8.7 Hz), 7.31 (1H, s), 7.13 (3H, m), 7.07 (2H, m), 5.49 (2H, br s), 3.91 (2H, s), 3.41 (4H, m), 3.27 (3H, s); HRMS calcd for $C_{26}H_{24}N_4O_6$+H$^+$: 489.1774. Found: 489.1778.

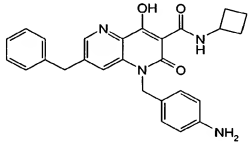
Example 71: *N*-Cyclobutyl-4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate and cyclobutylamine employing methods similar to those described in Example 2 and was

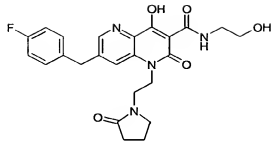
obtained as a white solid: ^{1}H NMR (d_6-DMSO) δ 10.91 (1H, d, J = 7.6 Hz), 8.21 (1H, s), 8.10 (2H, d, J = 8.6 Hz), 7.35 (2H, d, J = 8.6 Hz), 7.29 (1H, s), 7.14 (3H, m), 7.08 (2H, m), 5.47 (2H, br s), 4.40 (1H, m), 3.91 (2H, s), 2.24 (2H, m), 1.86 (2H, m), 1.67 (2H, m); HRMS calcd for $C_{27}H_{24}N_4O_5$+H$^+$: 485.1825. Found: 485.1815.

Example 72: 1-[(4-Aminophenyl)methyl]-*N*-cyclobutyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared by hydrogenation of *N*-cyclobutyl-4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide in THF in the presence of 3% Pt-C. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The product was obtained as a tan solid by addition of one equivalent of conc. HCl followed by concentration in vacuo and trituration with Et_2O: ^{1}H NMR (CD_3OD) δ 7.76 (1H, br), 7.32-7.27 (8H, m), 7.16 (2H, d, J = 7.5 Hz), 5.57 (2H, s), 4.57 (1H, m), 4.19 (2H, s), 2.44 (2H, m), 2.13 (2H, m), 1.86 (2H, m); HRMS calcd for $C_{27}H_{26}N_4O_3$+H$^+$: 455.2083. Found: 455.2088.

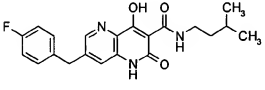
Example 73: 7-[(4-Fluorophenyl)methyl]-4-hydroxy-*N*-(2-hydroxyethyl)-2-oxo-1-[2-(2-oxo-1-pyrrolidinyl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide



This compound was prepared from ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate and 2-hydroxyethylamine by methods similar to those described in Example 6. The product was obtained as a white solid: ^{1}H NMR ($CDCl_3$) δ 10.38 (1H, br m), 8.60 (1H, s), 8.07 (1H, s), 7.24 (2H, m), 7.00 (2H, t, J = 8.6 Hz), 4.36 (2H, t, J = 7 Hz), 4.15 (2H, s), 3.87 (2H, t, J = 5 Hz), 3.66 (2H, m), 3.51 (2H, t, J = 8 Hz), 3.45 (2H, t, J = 7 Hz), 2.37 (2H, t, J = 8 Hz), 2.00 (2H, m).

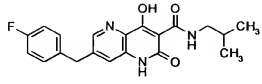
Examples 74 – 116 may be prepared by methods described herein or by any method known to one skilled in the art.

Example 74



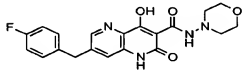
M+H calcd: 384.1723. M+H found 384.1721

Example 75



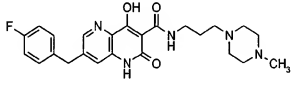
M+H calcd: 370.1567. M+H found: 370.1559

Example 76



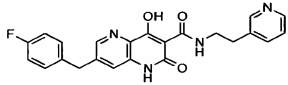
M+H calcd: 399.1469. M+H found: 399.1459

Example 77



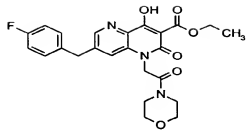
M+H calcd: 454.2254. M+H found: 454.2242

Example 78



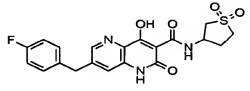
M+H calcd: 419.1519. M+H found: 419.1512

Example 79



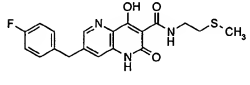
M+H calcd: 470.1727. M+H found: 470.1743

Example 80



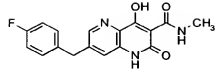
M+H calcd: 432.1029. M+H found: 432.1049

Example 81



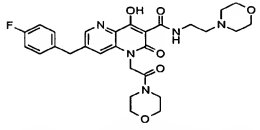
M+H calcd: 388.1131. M+H found: 388.1125

Example 82



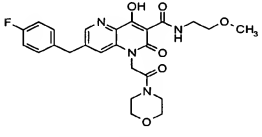
M+H calcd: 328.1097. M+H found: 328.1084

Example 83



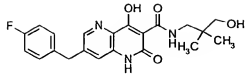
M+H calcd: 554.2415. M+H found: 554.1406

Example 84



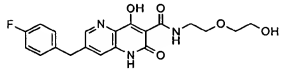
M+H calcd: 499.1993. M+H found: 499.1996

Example 85



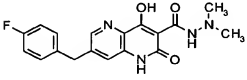
M+H calcd: 400.1672. M+H found: 400.1665

Example 86



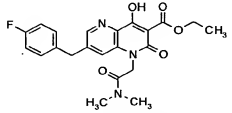
M+H calcd: 402.1465. M+H found: 402.1469

Example 87



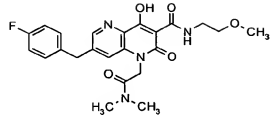
M+H calcd: 357.1363. M+H found: 357.1351

Example 88



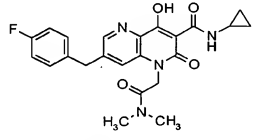
M+H calcd: 428.1622. M+H found: 428.1616

Example 89



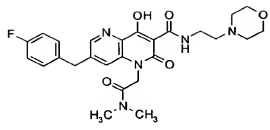
M+H calcd: 457.1887. M+H found: 457.1884

Example 90



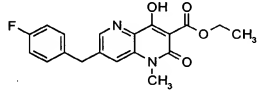
M+H calcd: 439.1781. M+H found: 439.1774

Example 91



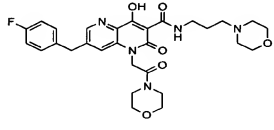
M+H calcd: 512.2309. M+H found: 512.2296

Example 92



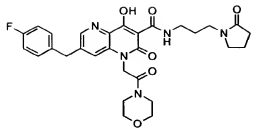
M+H calcd: 357.1250. M+H found: 357.1244

Example 93



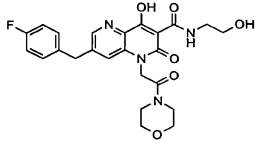
M+H calcd: 568.2571. M+H found: 568.2571

Example 94



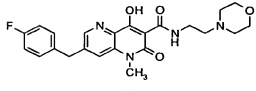
M+H calcd: 566.2415. M+H found: 566.2411

Example 95



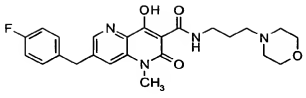
M+H calcd: 485.1836. M+H found: 485.1828

Example 96



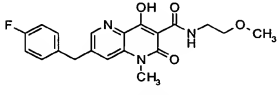
M+H calcd: 441.1938. M+H found: 441.1927

Example 97



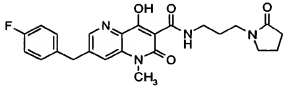
M+H calcd: 455.2095. M+H found: 455.2089

Example 98



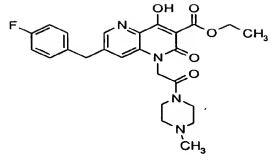
M+H calcd: 386.1516. M+H found: 386.1531

Example 99



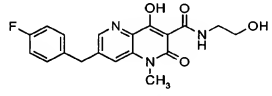
M+H calcd: 453.1938. M+H found: 453.1927

Example 100



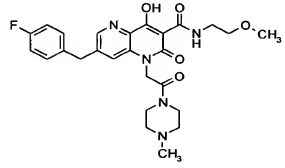
M+H calcd: 483.2043. M+H found: 483.2035

Example 101



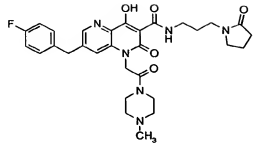
M+H calcd: 372.1359. M+H found: 372.1355

Example 102



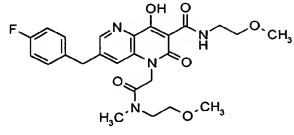
M+H calcd: 512.2309. M+H found: 512.2307

Example 103



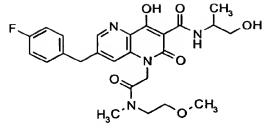
M+H calcd: 579.2734. M+H found: 579.2731

Example 104



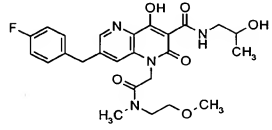
AP+ MS: 501 (M+H, 100)

Example 105



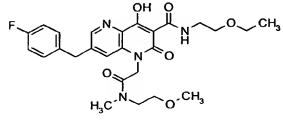
AP+ MS: 501 (M+H, 100)

Example 106



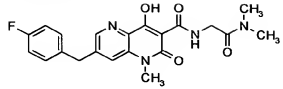
AP+ MS: 501 (M+H, 100)

Example 107



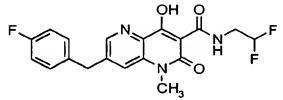
AP+ MS: 515 (M+H, 100)

Example 108



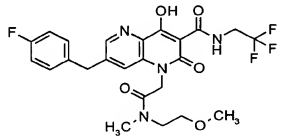
M+H calcd: 413.1625. M+H found: 413.1617

Example 109



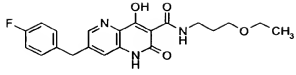
M+H calcd: 392.1222. M+H found: 392.1222

Example 110



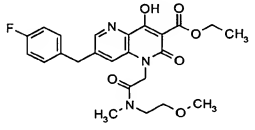
AP+ MS: 525 (M+H, 100)

Example 111



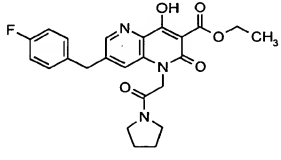
M+H calcd: 400.1673. M+H found: 400.1681

Example 112



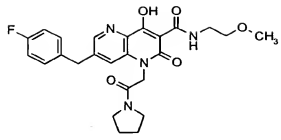
AP- MS: 470 (M-H, 100)

Example 113



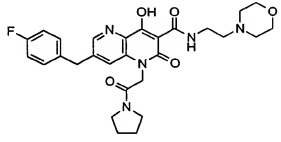
AP- MS: 452 (M-H, 100)

Example 114



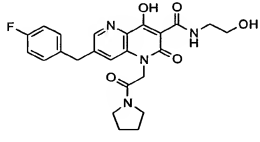
AP+ MS: 483 (M+H, 100)

Example 115



AP+ MS: 538 (M+H, 100)

Example 116



AP- MS: 467 (M-H, 100)

Example 117: Biological Activity

MT4 Cell Assay

Experimental Procedure

Antiviral HIV activity and compound-induced cytotoxicity were measured in parallel by means of a propidium iodide based procedure in the human T-cell lymphotropic virus transformed cell line MT4. Aliquots of the test compounds were serially diluted in medium (RPMI 1640, 10% fetal calf serum (FCS), and gentamycin) in 96-well plates (Costar 3598) using a Cetus Pro/Pette. Exponentially growing MT4 cells were harvested and centrifuged at 1000 rpm for 10 min in a Jouan centrifuge (model CR 4 12). Cell pellets were resuspended in fresh medium (RPMI 1640, 20% FCS, 20% IL-2, and gentamycin) to a density of 5 x 105 cells/ml. Cell aliquots were infected by the addition of HIV-1 (strain IIIB) diluted to give a viral multiplicity of infection of 100 x TCID50. A similar cell aliquot was diluted with medium to provide a mock-infected control. Cell infection was allowed to proceed for 1 hr at 37°C in a tissue culture incubator with humidified 5% CO_2 atmosphere. After the 1 hr incubation the virus/cell suspensions were diluted 6-fold with fresh medium, and 125 µl of the cell suspension was added to each well of the plate containing pre-diluted compound. Plates were then placed in a tissue culture incubator with humidified 5% CO_2 for 5 days. At the end of the incubation period, cell number and hence HIV-induced cytopathy was estimated by either (A) propidium iodide staining, or by an (B) MTS tetrazolium staining method (ref. 5).

For propidium iodide readout, 27 µl of 5% Nonidet-40 was added to each well of the incubation plate. After thorough mixing with a Costar multitip pipetter, 60 µl of the mixture was transferred to filter-bottomed 96-well plates. The plates were analyzed in an automated assay instrument (Screen Machine, Idexx Laboratories). The control and standard used was 3'-azido-3'-deoxythymidine tested over a

concentration range of 0.01 to 1 μM in every assay. The expected range of IC_{50} values for 3'-azido-3'-deoxythymidine is 0.04 to 0.12 μM. The assay makes use of a propidium iodide dye to estimate the DNA content of each well.

For MTS readout, 20 μl CellTiter 96 AQ One Solution reagent (Promega #G3582) was added to each well. At 75 minutes following the addition of MTS reagent, absobance was read at 492 nM using a Tecan Sunrise 96-well plate reader.

Analysis

The antiviral effect of a test compound is reported as an IC_{50}, i.e. the inhibitory concentration that would produce a 50% decrease in the HIV-induced cytopathic effect. This effect is measured by the amount of test compound required to restore 50% of the cell growth of HIV-infected MT4 cells, compared to uninfected MT4 cell controls. IC_{50} was calculated by RoboSage, Automated Curve Fitting Program, version 5.00, 10-Jul-1995.

For each assay plate, the results (relative fluorescence units, rfU, or OD values) of wells containing uninfected cells or infected cells with no compound were averaged, respectively. For measurements of compound-induced cytotoxicty, results from wells containing various compound concentrations and uninfected cells were compared to the average of uninfected cells without compound treatment. Percent of cells remaining is determined by the following formula:

Percent of cells remaining = (compound-treated uninfected cells, rfU, or OD values / untreated uninfected cells) x 100.

A level of percent of cells remaining of 79% or less indicates a significant level of direct compound-induced cytotoxicity for the compound at that concentration. When this condition occurs the results from the compound-treated infected wells at this concentration are not included in the calculation of IC_{50}.

For measurements of compound antiviral activity, results from wells containing various compound concentrations and infected cells are compared to the

average of uninfected and infected cells without compound treatment. Percent inhibition of virus is determined by the following formula:

Percent inhibition of virus = (1-((ave. untreated uninfected cells - treated infected cells) / (ave. untreated uninfected cells - ave. untreated infected cells)))x 100

References:

1. Averett, D.R., Anti-HIV compound assessment by two novel high capacity assays, *J. Virol. Methods* 23: 263-276, 1989.

2. Schwartz, O., et al,. A rapid and simple colorimetric test for the study of anti-HIV agents, *AIDS Res. and Human Retroviruses* 4 (6): 441-447, 1988..

3. Daluge, S.M., et al., 5-chloro-2'3'-deoxy-3'fluorouridine (935U83), a selective anti-human immunodeficiency virus agent with an improved metabolic and toxicological profile. *Antimicro. Agents and Chemother.* 38 (7): 1590-1603, 1994.

4. Dornsife, R.E., et al., Anti-human immunodeficiency virus synergism by zidovudine (3'-azidothymidine) and didanosine (dideoxyinosine) contrasts with the additive inhibition of normal human marrow progenitor cells, *Antimicro. Agents and Chemother.* 35 (2): 322-328, 1991.

5. Promega Technical Bulletin #TB245. CellTiter 96 AQ One Solution Cell Proliferation Assay.

Results

Compounds of the present invention have anti-HIV activity in the range IC_{50} = 1-1000 nM.

Example 118 Biological Activity

Pseudotyped HIV vector expressing luciferase reporter assay

Expression of luciferase reporter following viral integration was performed essentially as described in Jármy, G. et al., J. Medical Virology, 64:223-231, 2001.

Results

Compounds of the present invention have anti-HIV activity in this assay in the range $IC_{50} = 1 - 1000$ nM.

Table 1: IC_{50} values for representative compounds

Example number	IC_{50} (nM)
2	a*
9	a
10	a
12	a
17	b**
28	a
36	a
37	a
45	a
49	a
50	a
54	a
62	a
64	a
83	b
84	a
85	a
86	a
89	a
91	b
93	b
94	b
95	b
96	a
97	a
98	a
99	a

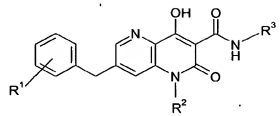
101	a
102	a
104	a
105	a
106	a
107	a

* $IC_{50} < 10$ nM

** $IC_{50} = 10 - 25$ nM

Claims

1. A compound of formula (I):



(I)

wherein:

R^1 is one or more substituents independently selected from hydrogen, hydroxy, CN, $N(R^aR^b)$, C_{1-8}alkyl, C_{3-7}cycloalkyl, halogen and C_{1-8}alkoxy;

R^2 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7}cycloalkenyl, C_{3-6} alkynyl, halogen, CN, NO_2, OR^a, $N(R^aR^b)$, $S(O)_mR^a$, SR^a, $OS(O)_mR^a$, $S(O)_mOR^a$, $OS(O)_mOR^a$, $N(R^a)S(O)_mR^b$, $S(O)_mN(R^aR^b)$, $N(R^a)S(O)_mN(R^aR^b)$, $OS(O)_mN(R^aR^b)$, $N(R^a)S(O)_mOR^b$, $C(O)R^a$, $OC(O)R^a$, $C(O)OR^a$, $OC(O)OR^a$, $N(R^a)C(O)R^b$, $C(O)N(R^aR^b)$, $N(R^a)C(O)N(R^aR^b)$, $OC(O)N(R^aR^b)$, $N(R^a)C(O)OR^b$, $C(NR^aR^b)=N(R^a)$, $N(R^a)C(NR^aR^b)=N(R^a)$, $C(SR^a)=N(R^b)$, $C(OR^a)=N(R^b)$, $N(R^a)C(SR^a)=N(R^b)$ and heterocycle optionally substituted with oxo or R^a;
or optionally when R^2 is C_{5-7} cycloalkyl, C_{6-14} aralkyl, C_{5-7} cycloalkenyl, C_{6-14} aryl or heterocycle R^2 may be fused to 5-7 membered carbocyclic or heterocyclic rings;

R^a and R^b are independently hydrogen, NO_2, OR^c, CN, $N(R^cR^d)$, $C(O)R^c$, $C(O)C(O)R^c$, $C(O)N(R^cR^d)$, $C(O)C(O)N(R^cR^d)$, $S(O)_mR^c$, SR^c, $S(O)_mN(R^cR^d)$, C_{1-8}

alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, CN, NO_2, OR^c, $N(R^cR^d)$, $S(O)_mR^c$, SR^c, $OS(O)_mR^c$, $S(O)_mOR^c$, $OS(O)_mOR^c$, $N(R^c)S(O)_mR^d$, $S(O)_mN(R^cR^d)$, $N(R^c)S(O)_mN(R^cR^d)$, $OS(O)_mN(R^cR^d)$, $N(R^c)S(O)_mOR^d$, $C(O)R^c$, $OC(O)R^c$, $C(O)OR^c$, $OC(O)OR^c$, $N(R^c)C(O)R^d$, $C(O)N(R^cR^d)$, $N(R^c)C(O)N(R^cR^d)$, $OC(O)N(R^cR^d)$, $N(R^c)C(O)OR^d$, $C(NR^cR^d)=N(R^c)$, $C(SR^c)=N(R^d)$, $C(OR^c)=N(R^d)$ and heterocycle;

Optionally, R^a and R^b may be linked together through one or more ring carbon atoms and/or ring heteroatoms including N, O, $C(R^cR^d)$, C(O), $S(O)_m$, or S to form a saturated or unsaturated 3 to 8 membered carbocyclic or heterocyclic ring;

R^c and R^d are independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

Optionally, R^c and R^d may be linked together through one or more ring carbon atoms and/or ring heteroatoms including N, O, C(O) and $S(O)_m$ or S to form a saturated or unsaturated 3 to 8 membered carbocyclic or heterocyclic ring;

R^3 is hydrogen, hydroxy, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, $N(R^aR^b)$, or heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, halogen, oxo, CN, NO_2, OR^a, $N(R^aR^b)$, $S(O)_mR^a$, SR^a, $OS(O)_mR^a$, $S(O)_mOR^a$, $OS(O)_mOR^a$, $N(R^a)S(O)_mR^b$, $S(O)_mN(R^aR^b)$, $N(R^a)S(O)_mN(R^aR^b)$, $OS(O)_mN(R^aR^b)$, $N(R^a)S(O)_mOR^b$, $C(O)R^a$, $OC(O)R^a$, $C(O)OR^a$, $OC(O)OR^a$, $N(R^a)C(O)R^b$, $C(O)N(R^aR^b)$, $N(R^a)C(O)N(R^aR^b)$, $OC(O)N(R^aR^b)$, $N(R^a)C(O)OR^b$, $C(NR^a)=N(R^b)$, $C(SR^a)=N(R^b)$, $C(OR^a)=N(R^b)$, $N(R^a)C(NR^aR^b)=N(R^a)$, $N(R^a)C(SR^a)=N(R^b)$, $N(R^a)C(OR^a)=N(R^b)$, and heterocycle optionally substituted by oxo or R^a;

m is 1 or 2;

or a pharmaceutically acceptable derivative thereof, provided that:

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl , C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, or R^2 is C_{1-8} alkyl substituted with $S(O)_mR^a$ where R^a is C_{1-8} alkyl and m is 2, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl.

2. A compound of formula (I) according to claim 1 wherein:

R^1 is hydrogen or halogen;

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl optionally substituted with C_{3-7}cycloalkyl, OR^a, $N(R^aR^b)$, $C(O)R^a$, $C(O)N(R^aR^b)$, or heterocycle optionally substituted with oxo or R^a; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ or R^a; wherein m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$;

wherein: R^a and R^b are independently hydrogen, OR^c, SR^c, C_{1-8}alkyl, C_{6-14}aryl or heterocycle, each of which each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, CN, NO_2, OR^c, $N(R^cR^d)$, $S(O)_mR^c$, SR^c, $OS(O)_mR^c$, $S(O)_mOR^c$, $OS(O)_mOR^c$, $N(R^c)S(O)_mR^d$, $S(O)_mN(R^cR^d)$, $N(R^c)S(O)_mN(R^cR^d)$, $OS(O)_mN(R^cR^d)$, $N(R^c)S(O)_mOR^d$, $C(O)R^c$, $OC(O)R^c$, $C(O)OR^c$, $OC(O)OR^c$, $N(R^c)C(O)R^d$, $C(O)N(R^cR^d)$, $N(R^c)C(O)N(R^cR^d)$, $OC(O)N(R^cR^d)$, $N(R^c)C(O)OR^d$, $C(NR^cR^d)=N(R^c)$, $C(SR^c)=N(R^d)$, $C(OR^c)=N(R^d)$ and heterocycle;

wherein R^c is hydrogen , C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

R^c and R^d are independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

or a pharmaceutically acceptable derivative thereof provided that

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl , C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl.

3. A compound of formula (I) according to claim 1 wherein:

R^1 is hydrogen or halogen;

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl optionally substituted with C_{3-7}cycloalkyl, OR^a, $N(R^aR^b)$, $C(O)R^a$, $C(O)N(R^aR^b)$, or heterocycle optionally substituted with oxo or R^a; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ or R^a; wherein m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$;

wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

wherein R^c is hydrogen, C_{1-8} alkyl or C_{6-14}aryl ;

or a pharmaceutically acceptable derivative thereof provided that

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl , C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl;

4. A compound of formula (I) according to claim 1 wherein:

R^1 is hydrogen or halogen;

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl substituted with C_{3-7}cycloalkyl, $C(O)R^a$ wherein R^a is heterocycle, or heterocycle optionally substituted with oxo; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ wherein R^a is C_{1-8}alkyl and m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a; wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

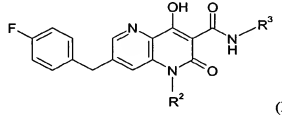
(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$ wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

wherein R^c is hydrogen, C_{1-8} alkyl or C_{6-14}aryl ;

or a pharmaceutically acceptable derivative thereof .

5. A compound of formula (Ia)



(Ia)

wherein:

R^2 is selected from hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, heterocycle, each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, halogen, CN, NO_2, OR^a, $N(R^aR^b)$, $S(O)_mR^a$, SR^a, $OS(O)_mR^a$, $S(O)_mOR^a$, $OS(O)_mOR^a$, $N(R^a)S(O)_mR^b$, $S(O)_mN(R^aR^b)$,

$N(R^a)S(O)_mN(R^aR^b)$, $OS(O)_mN(R^aR^b)$, $N(R^a)S(O)_mOR^b$, $C(O)R^a$, $OC(O)R^a$, $C(O)OR^a$, $OC(O)OR^a$, $N(R^a)C(O)R^b$, $C(O)N(R^aR^b)$, $N(R^a)C(O)N(R^aR^b)$, $OC(O)N(R^aR^b)$, $N(R^a)C(O)OR^b$, $C(NR^aR^b)=N(R^a)$, $N(R^a)C(NR^aR^b)=N(R^a)$, $C(SR^a)=N(R^b)$, $C(OR^a)=N(R^b)$, $N(R^a)C(SR^a)=N(R^b)$ and heterocycle optionally substituted with oxo or R^a;

or optionally when R^2 is C_{5-7} cycloalkyl, C_{6-14} aralkyl, C_{5-7} cycloalkenyl, C_{6-14} aryl or heterocycle R^2 may be fused to 5-7 membered carbocyclic or heterocyclic rings;

R^a and R^b are independently hydrogen, NO_2, OR^c, CN, $N(R^cR^d)$, $C(O)R^c$, $C(O)C(O)R^c$, $C(O)N(R^cR^d)$, $C(O)C(O)N(R^cR^d)$, $S(O)_mR^c$, SR^c, $S(O)_mN(R^cR^d)$, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, CN, NO_2, OR^c, $N(R^cR^d)$, $S(O)_mR^c$, SR^c, $OS(O)_mR^c$, $S(O)_mOR^c$, $OS(O)_mOR^c$, $N(R^c)S(O)_mR^d$, $S(O)_mN(R^cR^d)$, $N(R^c)S(O)_mN(R^cR^d)$, $OS(O)_mN(R^cR^d)$, $N(R^c)S(O)_mOR^d$, $C(O)R^c$, $OC(O)R^c$, $C(O)OR^c$, $OC(O)OR^c$, $N(R^c)C(O)R^d$, $C(O)N(R^cR^d)$, $N(R^c)C(O)N(R^cR^d)$, $OC(O)N(R^cR^d)$, $N(R^c)C(O)OR^d$, $C(NR^cR^d)=N(R^c)$, $C(SR^c)=N(R^d)$, $C(OR^c)=N(R^d)$ and heterocycle;

Optionally, R^a and R^b may be linked together through one or more ring carbon atoms and/or ring heteroatoms including N, O, $C(R^cR^d)$, C(O), $S(O)_m$, or S to form a saturated or unsaturated 3 to 8 membered carbocyclic or heterocyclic ring;

R^c and R^d are independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

Optionally, R^c and R^d may be linked together through one or more ring carbon atoms and/or ring heteroatoms including N, O, C(O) and $S(O)_m$ or S to form a saturated or unsaturated 3 to 8 membered carbocyclic or heterocyclic ring;

R^3 is hydrogen, hydroxy, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, $N(R^aR^b)$, or heterocycle, each of which may be optionally

substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, halogen, oxo, CN, NO_2, OR^a, $N(R^aR^b)$, $S(O)_mR^a$, SR^a, $OS(O)_mR^a$, $S(O)_mOR^a$, $OS(O)_mOR^a$, $N(R^a)S(O)_mR^b$, $S(O)_mN(R^aR^b)$, $N(R^a)S(O)_mN(R^aR^b)$, $OS(O)_mN(R^aR^b)$, $N(R^a)S(O)_mOR^b$, $C(O)R^a$, $OC(O)R^a$, $C(O)OR^a$, $OC(O)OR^a$, $N(R^a)C(O)R^b$, $C(O)N(R^aR^b)$, $N(R^a)C(O)N(R^aR^b)$, $OC(O)N(R^aR^b)$, $N(R^a)C(O)OR^b$, $C(NR^a)=N(R^b)$, $C(SR^a)=N(R^b)$, $C(OR^a)=N(R^b)$, $N(R^a)C(NR^aR^b)=N(R^a)$, $N(R^a)C(SR^a)=N(R^b)$, $N(R^a)C(OR^a)=N(R^b)$, and heterocycle optionally substituted by oxo or R^a;

m is 1 or 2;

or a pharmaceutically acceptable derivative thereof, provided that:

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl , C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, or R^2 is C_{1-8} alkyl substituted with $S(O)_mR^a$ where R^a is C_{1-8} alkyl and m is 2, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl.

6. A compound of formula (Ia) according to claim 5 wherein:

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl optionally substituted with C_{3-7}cycloalkyl, OR^a, $N(R^aR^b)$, $C(O)R^a$, $C(O)N(R^aR^b)$, or heterocycle optionally substituted with oxo or R^a; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ or R^a; wherein m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$;

wherein R^a and R^b are independently hydrogen, OR^c, SR^c, C_{1-8}alkyl, C_{6-14}aryl or heterocycle, each of which each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl, CN, NO_2, OR^c, $N(R^cR^d)$, $S(O)_mR^c$, SR^c, $OS(O)_mR^c$, $S(O)_mOR^c$, $OS(O)_mOR^c$, $N(R^c)S(O)_mR^d$, $S(O)_mN(R^cR^d)$, $N(R^c)S(O)_mN(R^cR^d)$, $OS(O)_mN(R^cR^d)$, $N(R^c)S(O)_mOR^d$, $C(O)R^c$, $OC(O)R^c$, $C(O)OR^c$, $OC(O)OR^c$, $N(R^c)C(O)R^d$, $C(O)N(R^cR^d)$, $N(R^c)C(O)N(R^cR^d)$, $OC(O)N(R^cR^d)$, $N(R^c)C(O)OR^d$, $C(NR^cR^d)=N(R^c)$, $C(SR^c)=N(R^d)$, $C(OR^c)=N(R^d)$ and heterocycle;
wherein R^c is hydrogen , C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

R^c and R^d are independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-7} cycloalkyl, C_{6-14} aralkyl, C_{2-6} alkenyl, C_{3-7} cycloalkenyl, C_{3-6} alkynyl, C_{6-14} aryl or heterocycle;

or a pharmaceutically acceptable derivative thereof provided that

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl , C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl.

7. A compound of formula (Ia) according to claim 5 wherein:

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl optionally substituted with C_{3-7}cycloalkyl, OR^a, $N(R^aR^b)$, $C(O)R^a$, $C(O)N(R^aR^b)$, or heterocycle optionally substituted with oxo or R^a; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ or R^a; wherein m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$;

wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

wherein R^c is hydrogen, C_{1-8} alkyl or C_{6-14}aryl;

or a pharmaceutically acceptable derivative thereof provided that

(a) when R^1 and R^2 are both hydrogen, then R^3 cannot be C_{1-8}alkyl substituted with $N(R^aR^b)$ where R^a and R^b are both C_{1-8} alkyl;

(b) when R^1 is halogen and R^2 is C_{1-8} alkyl , C_{1-8} alkyl substituted with $C(O)R^a$ where R^a is C_{1-8} alkyl, then R^3 cannot be C_{1-8} alkyl or C_{1-8} alkyl substituted with OR^a where R^a is C_{1-8} alkyl.

8. A compound of formula (Ia) according to claim 5 wherein:

R^2 is

(a) hydrogen;

(b) C_{1-8}alkyl substituted with C_{3-7}cycloalkyl, $C(O)R^a$ wherein R^a is heterocycle, or heterocycle optionally substituted with oxo; or

(c) C_{6-14}aralkyl optionally substituted with $S(O)_mR^a$ wherein R^a is C_{1-8}alkyl and m is 2;

R^3 is

(a) C_{1-8}alkyl optionally substituted with C_{1-8}alkyl, C_{3-7}cycloalkyl, OR^a, SR^a, $C(O)N(R^aR^b)$, $NR^aC(O)R^b$, or heterocycle optionally substituted with oxo or R^a; wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

(b) C_{3-7}cycloalkyl;

(c) C_{1-8}haloalkyl;

(d) heterocycle optionally substituted with oxo; or

(e) $N(R^aR^b)$ wherein R^a and R^b are independently hydrogen, NO_2, OR^c, $C(O)R^c$, C_{1-8}alkyl optionally substituted with OR^c, C_{6-14}aryl or heterocycle;

wherein R^c is hydrogen, C_{1-8} alkyl or C_{6-14}aryl ;

or a pharmaceutically acceptable derivative thereof.

9. A compound of formula (I) according to any of claims 1 – 4 wherein the pharmaceutically derivative is a salt.

10. A compound of formula (Ia) according to any of claims 5 – 8 wherein the pharmaceutically derivative is a salt.

11. A compound selected from the group consisting of:

Ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-(4-fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-benzyl-*N*-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Methyl 7-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-*N*,4-dihydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

N-Cyclopropyl-7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-morpholin-4-ylethyl)-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-4-hydroxy-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-*N*-(2-methylpropyl)-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cycloheptyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclopentyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclobutyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-*N*-[2-(methyloxy)ethyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-2-oxo-*N*-(2-phenylethyl)-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-2-oxo-*N*-(1-phenylethyl)-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-(Cyclohexylmethyl)-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-(2-Furanylmethyl)-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclohexyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-2-oxo-7-(phenylmethyl)-*N*-(2-thienylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclopropyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclobutyl-7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclopropyl-7-[(4-fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-*N*-(2-furanylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[3-(2-oxo-1-pyrrolidinyl)propyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[2-(1-pyrrolidinyl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

(±)-7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(tetrahydro-2-furnylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[2-(1-piperidinyl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(4-pyridinylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(2-pyridinylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-(3-pyridinylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-*N*-(hexahydro-1*H*-azepin-1-yl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-*N*-[2-(4-morpholinyl)ethyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(5-Fluoro-2-pyridinyl)methyl]-4-hydroxy-*N*-[3-(4-morpholinyl)propyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[2-(2-pyridinyl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-[(4-Fluorophenyl)methyl]-4-hydroxy-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

Benzyl-*N*-cyclobutyl-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-*N*-cyclopropyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-*N*-cyclobutyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-*N*-(2-furylmethyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-4-hydroxy-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-*N*-cyclopropyl-4-hydroxy-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-1-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-1-(cyclopropylmethyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-*N*-cyclobutyl-1-(cyclopropylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide ;

Ethyl 7-benzyl-4-hydroxy-1-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-*N*-cyclobutyl-4-hydroxy-1-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-*N*-(3-morpholin-4-ylpropyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(2-pyrrolidin-1-ylethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-benzyl-4-hydroxy-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-Benzyl-*N*-cyclobutyl-4-hydroxy-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 7-(4-fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(pyridin-4-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-2-oxo-*N*-(pyridin-3-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-1-[4-(methylsulfonyl)benzyl]-*N*-(2-morpholin-4-ylethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

Ethyl 4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxylate;

N-(2-Furanylmethyl)-4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

4-Hydroxy-*N*-[2-(methyloxy)ethyl]-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

N-Cyclobutyl-4-hydroxy-1-[(4-nitrophenyl)methyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

1-[(4-Aminophenyl)methyl]-*N*-cyclobutyl-4-hydroxy-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

and pharmaceutically acceptable salts thereof.

12. A compound selected from the group consisting of:
7-(4-fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
N-Cyclopropyl-7-(4-fluorobenzyl)-4-hydroxy-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-morpholin-4-ylethyl)-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-(2-morpholin-4-yl-2-oxoethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
4-Hydroxy-*N*-[2-(methyloxy)ethyl]-2-oxo-7-(phenylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-[(4-Fluorophenyl)methyl]-4-hydroxy-2-oxo-*N*-[3-(2-oxo-1-pyrrolidinyl)propyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-[(4-Fluorophenyl)methyl]-4-hydroxy-*N*-[2-(4-morpholinyl)ethyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-[(5-Fluoro-2-pyridinyl)methyl]-4-hydroxy-*N*-[3-(4-morpholinyl)propyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-1-[(1-methyl-1*H*-imidazol-2-yl)methyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-Benzyl-1-(cyclopropylmethyl)-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
7-Benzyl-4-hydroxy-*N*-(2-methoxyethyl)-2-oxo-1-(1,3-thiazol-2-ylmethyl)-1,2-dihydro-1,5-naphthyridine-3-carboxamide;

7-(4-Fluorobenzyl)-4-hydroxy-*N*-(2-methoxyethyl)-1-[4-(methylsulfonyl)benzyl]-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide;
and pharmaceutically acceptable salts thereof.

13. A compound selected from the group consisting of example numbers 2, 9, 10, 12, 17, 28, 36, 37, 45, 49, 50, 54, 62, 64, 83, 84, 85, 86, 89, 91, 93, 94, 95, 96, 97, 98, 99, 101, 102, 104, 105, 106, 107 and pharmaceutically acceptable salts thereof.

14. A compound selected from the group consisting of example numbers 12, 36, 37, 49, 84, 89, 91, 93, 95, 96, 101 and pharmaceutically acceptable salts thereof.

15. A method of treatment of a viral infection in a human comprising administering to said human an antiviral effective amount of a compound according to any of claims 1 to 14.

16. A method according to claim 15 wherein the viral infection is a HIV infection.

17. A compound as claimed in any of claims 1 to 14 for use in medical therapy.

18. Use of a compound as claimed in any of claims 1 to 14 in the manufacture of a medicament for the treatment or prophylaxis of a virus infection.

19. The use according to claim 18 wherein the viral infection is a HIV infection.

20. A pharmaceutical composition comprising an effective amount of a compound according to any of claims 1 to 14 together with a pharmaceutically acceptable carrier.

21. A pharmaceutical composition according to claim 20 in the form of a tablet or capsule.

22. A pharmaceutical composition according to claim 20 in the form of a liquid or suspension.

23. A method of treatment of a viral infection in a human comprising administering to said human a composition comprising a compound according to any of claims 1 to 14 and another therapeutic agent.

24. The method according to claim 23 wherein the viral infection is an HIV infection.

25. A composition according to claim 20, wherein said composition comprises at least one additional therapeutic agent selected from the group consisting of (1-alpha, 2-beta, 3-alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514, lobucavir], 9-[(2R,3R,4S)-3,4-bis(hydroxymethyl)-2-oxetanosyl]adenine (oxetanocin-G), TMC-114, BMS-232632, acyclic nucleosides [e.g. acyclovir, valaciclovir, famciclovir, ganciclovir, penciclovir), acyclic nucleoside phosphonates [e.g. (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC), [[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]phosphinylidene]bis(oxymethylene)-2,2-dimethylpropanoic acid (bis-POM PMEA, adefovir dipivoxil), [[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid (tenofovir), (R)-[[2-(6-Amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid bis-(isopropoxycarbonyloxymethyl)ester (bis-POC-PMPA)], ribonucleotide reductase inhibitors (e.g. 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl) thiocarbonohydrazone and hydroxyurea), nucleoside reverse transcriptase inhibitors (e.g. , 3'-azido-3'-deoxythymidine (AZT, zidovudine), 2',3'-dideoxycytidine (ddC, zalcitabine), 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine (ddI, didanosine), 2',3'-didehydrothymidine (d4T, stavudine), (-)-

beta-D-2,6-diaminopurine dioxolane (DAPD), 3'-Azido-2',3'-dideoxythymidine-5'-H-phosphophonate (phosphonovir), 2'-deoxy-5-iodo-uridine (idoxuridine), as (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine), or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), , 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), ABT-606 (2HM-H2G) and ribavirin), protease inhibitors (e.g. indinavir, ritonavir, nelfinavir, amprenavir, saquinavir, (R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-(isoquinolin-5-yloxyacetyl)amino-3-methylthiopropanoyl]amino-4-phenylbutanoyl]-5,5- dimethyl-1,3-thiazolidine-4-carboxamide (KNI-272), 4R-(4alpha,5alpha,6beta)]-1,3-bis[(3-aminophenyl)methyl]hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-one dimethanesulfonate (mozenavir), 3-[1-[3-[2-(5-trifluoromethylpyridinyl)-sulfonylamino]phenyl]propyl]-4- hydroxy-6alpha-phenethyl-6beta-propyl-5,6-dihydro-2-pyranone (tipranavir), N'-[2(S)-Hydroxy-3(S)-[N-(methoxycarbonyl)-l-tert-leucylamino]-4- phenylbutyl-N ^{alpha}-(methoxycarbonyl)-N'-[4-(2-pyridyl)benzyl]-L- tert-leucylhydrazide (BMS-232632), 3-(2(S)-Hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-phenylbutanoyl)-5,5-dimethyl-N-(2-methylbenzyl)thiazolidine-4(R)-carboxamide (AG-1776), N-(2(R)-Hydroxy-1(S)-indanyl)-2(R)-phenyl-methyl-4(S)-hydroxy-5-(1-(1-(4-benzo[b]furanylmethyl)-2(S)-N'-(tert-butylcarboxamido)piperazinyl)pentanamide (MK-944A), and GW 433908), interferons such as α-interferon, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyridamole; pentoxifylline, N-acetylcysteine (NAC), Procysteine, α -trichosanthin, phosphonoformic acid, as well as immunomodulators such as interleukin II or thymosin, granulocyte macrophage colony stimulating factors, erythropoetin, soluble CD_4 and genetically engineered derivatives thereof, non-nucleoside reverse transcriptase inhibitors (NNRTIs) for example, TMC-120, TMC-125, nevirapine (BI-RG-587), alpha-((2-acetyl-5-methylphenyl)amino)-2,6-dichloro-benzeneacetamide (loviride), 1-[3-

(isopropylamino)-2-pyridyl]-4-[5-(methanesulfonamido)-1H-indol-2-ylcarbonyl]piperazine monomethanesulfonate (delavirdine), (10R, 11S, 12S)-12-Hydroxy-6, 6, 10, 11-tetramethyl-4-propyl-11,12-dihydro-2H, 6H, 10H-benzo(1, 2-b:3, 4-b':5, 6-b")tripyran-2-one ((+) calanolide A), (4S)-6-Chloro-4-[1E)-cyclopropylethenyl)-3,4- dihydro-4-(trifluoromethyl)-2(1H)-quinazolinone (DPC-083), 1-(ethoxymethyl)-5-(1-methylethyl)-6-(phenylmethyl)-2,4(1H,3H)-pyrimidinedione (MKC-442), 5-(3,5-dichlorophenyl)thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbamate (capravirine), glycoprotein 120 antagonists [e.g. PRO-2000, PRO-542 and 1,4-bis[3-[(2, 4-dichlorophenyl)carbonylamino]-2-oxo-5,8-disodiumsulfanyl]naphthalyl-2, 5-dimethoxyphenyl-1, 4-dihydrazone (FP-21399)], cytokine antagonists [e.g. reticulose (Product-R), 1,1'-azobis-formamide (ADA), and 1,11-(1,4-phenylenebis(methylene))bis-1,4,8,11-tetraazacyclotetradecane octahydrochloride (AMD-3100)], and fusion inhibitors for example T-20 and T-124.

26. A method according to claim 23, wherein said therapeutic agent is selected from the group consisting of (1-alpha, 2-beta, 3-alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514, lobucavir], 9-[(2R,3R,4S)-3,4-bis(hydroxymethyl)-2-oxetanosyl]adenine (oxetanocin-G), acyclic nucleosides [e.g. acyclovir, valaciclovir, famciclovir, ganciclovir, penciclovir), acyclic nucleoside phosphonates [e.g. (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC), [[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]phosphinylidene]bis(oxymethylene)-2,2-dimethylpropanoic acid (bis-POM PMEA, adefovir dipivoxil), [[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid (tenofovir), (R)-[[2-(6-Amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid bis-(isopropoxycarbonyloxymethyl)ester (bis-POC-PMPA)], ribonucleotide reductase inhibitors (e.g. 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl) thiocarbonohydrazone and hydroxyurea), nucleoside reverse transcriptase inhibitors (e.g. , 3'-azido-3'-deoxythymidine (AZT, zidovudine),

2',3'-dideoxycytidine (ddC, zalcitabine), 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine (ddI, didanosine), 2',3'-didehydrothymidine (d4T, stavudine), (-)-beta-D-2,6-diaminopurine dioxolane (DAPD), 3'-Azido-2',3'-dideoxythymidine-5'-H-phosphophonate (phosphonovir), 2'-deoxy-5-iodo-uridine (idoxuridine), as (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine), or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), , 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), ABT-606 (2HM-H2G) and ribavirin), protease inhibitors (e.g. indinavir, ritonavir, nelfinavir, amprenavir, saquinavir, (R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-(isoquinolin-5-yloxyacetyl)amino-3-methylthiopropanoyl]amino-4-phenylbutanoyl]-5,5- dimethyl-1,3-thiazolidine-4-carboxamide (KNI-272), 4R-(4alpha,5alpha,6beta)]-1,3-bis[(3-aminophenyl)methyl]hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-one dimethanesulfonate (mozenavir), 3-[1-[3-[2-(5-trifluoromethylpyridinyl)-sulfonylamino]phenyl]propyl]-4- hydroxy-6alpha-phenethyl-6beta-propyl-5,6-dihydro-2-pyranone (tipranavir), N'-[2(S)-Hydroxy-3(S)-[N-(methoxycarbonyl)-l-tert-leucylamino]-4- phenylbutyl-N ^{alpha}-(methoxycarbonyl)-N'-[4-(2-pyridyl)benzyl]-L- tert-leucylhydrazide (BMS-232632), 3-(2(S)-Hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-phenylbutanoyl)-5,5-dimethyl-N-(2-methylbenzyl)thiazolidine-4(R)-carboxamide (AG-1776), N-(2(R)-Hydroxy-1(S)-indanyl)-2(R)-phenyl-methyl-4(S)-hydroxy-5-(1-(1-(4-benzo[b]furanylmethyl)-2(S)-N'-(tert-butylcarboxamido)piperazinyl)pentanamide (MK-944A), and GW 433908), interferons such as α-interferon, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyridamole; pentoxifylline, N-acetylcysteine (NAC), Procysteine, α -trichosanthin, phosphonoformic acid, as well as immunomodulators such as interleukin II or thymosin, granulocyte macrophage colony stimulating factors, erythropoetin, soluble CD_4 and genetically engineered derivatives thereof, non-nucleoside reverse transcriptase inhibitors (NNRTIs) [e.g.

nevirapine (BI-RG-587), alpha-((2-acetyl-5-methylphenyl)amino)-2,6-dichloro-benzeneacetamide (loviride), 1-[3-(isopropylamino)-2-pyridyl]-4-[5-(methanesulfonamido)-1H-indol-2-ylcarbonyl]piperazine monomethanesulfonate (delavirdine), (10R, 11S, 12S)-12-Hydroxy-6, 6, 10, 11-tetramethyl-4-propyl-11,12-dihydro-2H, 6H, 10H-benzo(1, 2-b:3, 4-b':5, 6-b")tripyran-2-one ((+) calanolide A), (4S)-6-Chloro-4-[1E)-cyclopropylethenyl)-3,4- dihydro-4-(trifluoromethyl)-2(1H)-quinazolinone (DPC-083), 1-(ethoxymethyl)-5-(1-methylethyl)-6-(phenylmethyl)-2,4(1H,3H)-pyrimidinedione (MKC-442), 5-(3,5-dichlorophenyl)thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbamate (capravirine)], glycoprotein 120 antagonists [e.g. PRO-2000, PRO-542 and 1,4-bis[3-[(2, 4-dichlorophenyl)carbonylamino]-2-oxo-5,8-disodiumsulfanyl]naphthalyl-2, 5-dimethoxyphenyl-1, 4-dihydrazone (FP-21399)], cytokine antagonists [e.g. reticulose (Product-R), 1,1'-azobis-formamide (ADA), and 1,11-(1,4-phenylenebis(methylene))bis-1,4,8,11-tetraazacyclotetradecane octahydrochloride (AMD-3100)], and fusion inhibitors (e.g. T-20 and T-1249).

ABSTRACT

The present infention features compounds that are HIV integrase inhibitors and therefore are useful in the inhibition of HIV replication, the prevention and/or treatment of infection by HIV, and in the treatment of AIDS and/or ARC.